Periodic Benefit-Risk Evaluation Report	
Medicinal Product	COVID-19 VACCINE ASTRAZENECA (AZD1222)
Date	28 February 2022

COVID-19 VACCINE ASTRAZENECA (AZD1222)

VAXZEVRIA™

Periodic Benefit-Risk Evaluation Report

Period covered: 29 June 2021 to 28 December 2021

International birth date: 29 December 2020 (United Kingdom)

Note: This report contains unblinded clinical trial adverse event data.

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The content of this Periodic Benefit-Risk Evaluation Report has been reviewed and endorsed by:	[redacted] Qualified Person for Pharmacovigilance in the EU	Electronic signature is available at the end of the document

EXECUTIVE SUMMARY

- **Introduction:** This Periodic Benefit-Risk Evaluation Report (PBRER) for COVID-19 VACCINE ASTRAZENECA (AZD1222/VAXZEVRIA™) summarises safety and efficacy/effectiveness data received and evaluated by AstraZeneca from 29 June 2021 to 28 December 2021, and places it in the context of the cumulative data and the overall benefit-risk profile.
- **Medicinal product:** COVID-19 VACCINE ASTRAZENECA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of Hunan-Hu-1 strain of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses. COVID-19 VACCINE ASTRAZENECA is indicated for active immunization of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19). COVID-19 VACCINE ASTRAZENECA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. The COVID-19 VACCINE ASTRAZENECA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of COVID-19 VACCINE ASTRAZENECA complete the vaccination course with COVID-19 VACCINE ASTRAZENCA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with COVID-19 VACCINE ASTRAZENECA at least 3-months after completing the primary 2-dose vaccination course (homologous boosting). During the Late-breaking period, the Core Data Sheet (CDS) was updated to note that COVID-19 VACCINE ASTRAZENECA may be given as a booster dose after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).
- **Marketing approvals:** As of 28 December 2021, COVID-19 VACCINE ASTRAZENECA has been approved for conditional marketing authorisation or emergency use authorisation in 93 countries. In addition, COVID-19 VACCINE ASTRAZENECA is also either approved or authorized for emergency use in more than 45 markets (duplicate licenses in some markets) managed by AstraZeneca partners – Serum Institute of India (SII), R-pharm, Fiocruz, and Verity Pharmaceuticals. COVID-19 VACCINE ASTRAZENECA is distributed via COVID-19 Vaccines Global Access (COVAX), in collaboration with United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO), under a World Health Organization (WHO) Emergency Use Listing to more than 80 countries.
- **Actions taken or proposed for safety reasons:**
    - AstraZeneca updated CDS Section 4.4 (Special warnings and special precautions for use) to include Cerebrovascular sinus thrombosis (CVST) without thrombocytopenia and Hypersensitivity reaction.
    - AstraZeneca added CVST without thrombocytopenia as an Important potential risk in the Core Risk Management Plan (RMP) for COVID-19 VACCINE ASTRAZENECA.

- AstraZeneca received impositions from various global regulatory authorities to include Capillary Leak Syndrome (CLS), Guillain-Barré Syndrome (GBS), Transverse myelitis, and Thrombocytopenia, including immune thrombocytopenia, in Sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) in local labelling.
- AstraZeneca updated European Union (EU) RMP to include GBS and Thrombocytopenia, including immune thrombocytopenia as Important identified risks.
- Health Authority impositions required issuance of Direct Healthcare Professional Communication (DHPC) letters for thrombocytopenia (including immune thrombocytopenia) with or without associated bleeding and CLS in various jurisdictions.

- **Safety changes to Reference Safety Information:** During this reporting period, AstraZeneca updated the COVID-19 VACCINE ASTRAZENECA CDS to include the following safety related changes:
  - On 02 November 2021, Section 4.4 (Special warnings and special precautions for use) was updated to 1) include clarifying language surrounding Hypersensitivity including anaphylaxis, 2) add information regarding reporting rates of Thrombosis with Thrombocytopenia Syndrome after second dose of COVID-19 VACCINE ASTRAZENECA, and 3) add information regarding CVST without thrombocytopenia.
  - On 02 November 2021, Section 4.8 (Undesirable effects) was updated to add information regarding observed reactogenicity in patients receiving a booster dose of COVID-19 VACCINE in COV001.
- **Estimated cumulative exposure of clinical trial subjects:** Approximately 60518 health volunteers have been enrolled into the clinical development programme, of which approximately 35567 have received at least one dose of AZD1222.
- **Estimated cumulative and reporting period patient exposure from post-approval (marketing) experience:** AstraZeneca is working directly with health departments in individual countries to determine the number of doses administered. Presently, administration data is available from the European Union, United Kingdom, Australia, Philippines, India, Canada, Argentina, Bangladesh, Brazil, Chile, Guatemala, Lebanon, Malaysia, and Uruguay. The cumulative number of doses administered in these territories/regions was confirmed as being over 1.60 billion doses. The number of doses distributed globally are over 2.4 billion doses cumulatively.
- **Late-breaking information:** Post the data-lock for this PBRER, AstraZeneca updated the CDS with the following additional safety-related changes:
  - On 06 January 2022, Section 4.6 (Pregnancy and lactation) was updated to reflect current safety data regarding vaccine administration in pregnancy women. The recommendation was updated to consider the use

of COVID-19 VACCINE ASTRAZENECA during pregnancy when the benefits outweigh the risks.

- On 17 January 2022, Section 4.6 (Pregnancy and lactation) was further updated to reflect current safety data regarding vaccine administration in lactating/breastfeeding women.
- On 04 February 2022, Section 4.2 (Posology and method of administration), Section 4.4 (Special warnings and special precautions for use) and Section 4.8 (Undesirable effects) were updated to support changes to the recommendation for use of COVID-19 VACCINE ASTRAZENECA as a booster dose (third dose) after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).

- AstraZeneca has validated signals of hypoaesthesia/paraesthesia and GBS. CDS Section 4.8 is currently under revision to include hypoaesthesia and paraesthesia as Adverse Drug Reactions (ADRs) and this is in the late-stage of being finalized. AstraZeneca is further reviewing GBS as per internal signal evaluation processes. Conclusions and any recommended actions will be communicated in the next PSUR.

- **Summary of overall benefit-risk evaluation:** The clinical benefit demonstrated in clinical trials, combined with the overall safety profile of COVID-19 VACCINE ASTRAZENECA has established a positive benefit-risk profile.

  The data received during the reporting period do not indicate a change in this positive benefit-risk profile for the approved indication. During the reporting interval AstraZeneca updated the Core RMP to include CVST without thrombocytopenia as an Important potential risk. Due to impositions, AstraZeneca updated the EU RMP to include GBS and Thrombocytopenia, including immune thrombocytopenia as Important identified risks for COVID-19 VACCINE ASTRAZENECA.

- **Conclusions and actions**: It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for COVID-19 VACCINE ASTRAZENECA.

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Regional Appendix R3	Summary of Ongoing Safety Concerns in the European Union
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Regional Appendix R7	US Prescribing Information
Regional Appendix R8	Combination Product Five-day and Malfunction Report Analysis

LIST OF ABBREVIATIONS

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or special term	Explanation
ACCP	American College of Chest Physicians
ACE	Angiotensin Converting Enzyme
ACO	Addendum to the Clinical Overview
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AEs	Adverse Events
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
AIH	Autoimmune Hepatitis
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	Autoimmune Disease Antibodies
AMN	Acute Macular Neuroretinopathy
AMOR	Acute Macular Outer Retinopathy
ANA	Antinuclear antibody
ANCA	Antineutrophil Cytoplasmic Antibodies
AOSD	Adult-onset Still's Disease
APLS	Antiphospholipid Syndrome
ARDS	Acute Respiratory Distress Syndrome
ARS	Agenzia Regionale di Sanità
AST	Aspartate Aminotransferase
AV	Atrioventricular
AZ	AstraZeneca
AZOOR	Acute Zonal Occult Outer Retinopathy
AZOR	Acute Zonal Outer Retinopathy
BC	Brighton Criteria
BCC	Brighton Collaboration Criteria
BG	Background
BLAST	Basic Local Alignment Search Tool
BRCA1	Breast Cancer Gene 1
CABG	Coronary Artery Bypass Graft
CCC	Company Clinical Comment

Abbreviation or special term	Explanation
CDC	Centres for Disease Control and Prevention
CDS	Core Data Sheet
ChAdOx1	Chimpanzee Adenovirus
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLS	Capillary Leak Syndrome
CMV	Cytomegalovirus
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CTPA	CT Pulmonary Angiogram
CU	Cutaneous
CV	Cardiovascular
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DCR	Data Correction Request
DHPC	Direct Healthcare Professional Communication
DIBD	Development International Birth Date
DIC	Disseminated Intravascular Coagulation
DILI	Drug Induced Liver Injury
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
EAR	Auricular
EAS	Enhanced Active Surveillance
EBV	Epstein–Barr virus
ED	Emergency Department
EEA	European Economic Area
EEG	Electroencephalography

Abbreviation or special term	Explanation
EF	Ejection Fraction
EKG	Electrocardiogram
EMA/EMEA	European Medicines Agency
ES_SIDIAP_PC	Spain Information System for the Development of Research in Primary Care
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorizations
EVDAS	EudraVigilance Data Analysis System
F	Female
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLAIR	Fluid-Attenuated Inversion Recovery
FSI	First Subject In
FVS	Fully Vaccinated Analysis Set
GBS	Guillain-Barre syndrome
GCS	Glasgow Coma Scale
GE	Gastroenteral
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAV	Hepatitis A Virus
HBV	Hepatitis B virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HD	Hospitalization
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HIT	Heparin-Induced Thrombocytopenia
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HLT	High Level Term
IBD	International Birth Date
IC	Intracardiac
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation or special term	Explanation
ICS	Intracavernous
ICSR	Individual Case Safety Reports
ICU	Intensive Care Unit
IF	Infiltration
IFA	Immunofluorescence Assay
IfH	Interface Hepatitis
IgG	Immunoglobin
IH	Respiratory (inhalation)
IJ	Intra-articular
IL	Interleukin
IM	Intramuscular
IMD	Immune-Mediated Diseases
IMEN	Intrameningeal
IMID	Immunomodulators
IN	Nasal
INR	International Normalized Ratio
IOC	Intraocular
IR	Incidence Rate
IS	Intradiscal (intraspinal)
ISTH	The International Society on Thrombosis and Haemostasis
ISYN	Intrasynovial
IV	Intravenous
IVIG	Intravenous Immunoglobulin
JIA	Juvenile Idiopathic Arthritis
LD	Low Dose
LDH	Lactate Dehydrogenase
LDSD	1 low dose and 1 standard dose
LETM	Longitudinal extensive transverse myelitis
LFTs	Liver function tests
LGI	Leucine-rich gliomain activated
LKM	Liver-Kidney Microsomal Antibody
LP	Lumbar Puncture
LpI	Lymphoplasmacytic infiltrate
LSO	Last Subject Out
LT	Life Threatening

Abbreviation or special term	Explanation
LV	Left Ventricular
M	Male
MAH	Marketing Authorisation Holder
MB	Myocardial Band
MC	Medically confirmed
ME	Myalgic Encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MELAS	Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes
MenACWY	Meningococcal Vaccine
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS-C/A	Multisystem Inflammatory Syndrome In Children/Adults
MOG-IGG	Anti-Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
MSSR	Monthly Summary Safety Report
NA	Neuralgic Amyotrophy
NAbs	Neutralizing Antibodies
NC	Non-confirmed
NEC	Necrotizing Enterocolitis
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIPH	Norwegian Institute of Public Health
NMOSD	Neuromyelitis Optica spectrum disorder
NOS	Not Otherwise Specified
NS	Non-Serious
NSAIDs	Non-steroidal Anti-inflammatory Srugs
O/E	Observed/Expected
OCT	Optical Coherence Tomography
OHDSI	Observational Health Data Science and Informatics
PAHO	Pan American Health Organization
PAM	Post-Authorisation Measure
PAMM	Paracentral Acute Middle Maculopathy
PAR	Parenteral
PASS	Post-Authorisation Safety Study

Abbreviation or special term	Explanation
PBRER	Periodic Benefit-Risk Evaluation Report
PBC	Primary Biliary Cholangitis
PE	Pulmonary Embolism
PET	Positron Emission Tomography
PF4	Platelet Factor 4
PI	Prescribing Information
PO	Oral
PRAC	Pharmacovigilance Risk Assessment Committee
PSC	Primary Sclerosing Cholangitis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTT	Partial Thromboplastin Time
PU	Intravenous bolus
PVFS	Post Viral Fatigue Syndrome
PY	Person Years
RBD	Receptor-Binding Domain
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RoH	Rosetting of hepatocytes
RoR	Reporting Odds Ratio
RT-PCR	Real-Time Polymerase Chain Reaction
RW	Risk Window
S	Serious
s	Seconds
SA	South Africa
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SCON	Subconjunctival
SCRI	Self-Controlled Risk Interval
SD	Standard Dose
SDSD	2 Standard Doses
SII	Serum Institute of India
SIRS	Systemic Inflammatory Response Syndrome

Abbreviation or special term	Explanation
SLA	Soluble Liver Antigen
SLE	Systemic Lupus Erythematosus
SMA	Smooth Muscle Antibody
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOT	Solid Organ Transplantation
SQ	Subcutaneous
SSC	Scientific and Standardisation Committee
SSI	Staten Serum institute
TCP	Thrombocytopenia
TCR	T cell Receptors
TGA	Therapeutic Goods Administration
THIN	The Health Improvement Network
TM	Transverse Myelitis
TPL	Transplacental
TPMT	Thiopurine Methyltransferase
TSH	Thyroid-Stimulating Hormone
TTO	Time To Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
UKHSA	UK Health Securities Agency
ULN	Upper Limit Of Normal
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
Unk	Unknown
USA/US	United States of America/United States
UTI	Urinary Tract Infection
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VID	Valencia Integrated Database
VIPER	Vaccines International Pregnancy Exposure Registry
VITT	Vaccine-Induced Thrombotic Thrombocytopenia

Abbreviation or special term	Explanation
WCN	World Congress of Neurology
WFN	World Federation of Neurology
WHO	World Health Organization
Y	Yes
yrs	Years

1 INTRODUCTION

This Periodic Benefit-Risk Evaluation Report (PBRER) prepared by AstraZeneca for coronavirus disease 2019 (COVID-19) VACCINE ASTRAZENECA (AZD1222/VAXZEVRIA™) summarises the safety and efficacy/effectiveness information received and evaluated by AstraZeneca from worldwide sources between 29 June 2021 and 28 December 2021. It is compiled in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C(R2) PBRER guideline and European Union (EU) Good Pharmacovigilance Practices Module VII (Revision 1); the terms/terminology used in this report are consistent with this guidance, and applicable international regulatory requirements.

The COVID-19 VACCINE ASTRAZENECA International Birth Date (IBD) is 29 December 2020.

COVID-19 VACCINE ASTRAZENECA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of Hunan-Hu-1 strain of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

COVID-19 VACCINE ASTRAZENECA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. The COVID-19 VACCINE ASTRAZENECA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of COVID-19 VACCINE ASTRAZENECA complete the vaccination course with COVID-19 VACCINE ASTRAZENCA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with COVID-19 VACCINE ASTRAZENECA at least 3-months after completing the primary 2-dose vaccination course (homologous boosting). During the Late-breaking period, the Core Data Sheet (CDS) was updated to note that COVID-19 VACCINE ASTRAZENECA may be given as a booster dose after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting) (see section 14).

COVID-19 VACCINE ASTRAZENECA is indicated for active immunisation of individuals ≥18 years for the prevention of COVID-19.

The inclusion of any information relating to a validated signal, important potential risk, or missing information within this PBRER should not be taken to imply that a causal association with the use of COVID-19 VACCINE ASTRAZENECA has been established.

2 WORLDWIDE MARKETING APPROVAL STATUS

COVID-19 VACCINE ASTRAZENECA was first approved for active immunisation of individuals ≥18 years for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received conditional marketing authorisation in the EU on 29 January 2021.

AZD1222 has been approved for conditional marketing authorisation or emergency use authorisation in 93 countries. In addition, COVID-19 VACCINE ASTRAZENECA is also either approved or authorized for emergency use in more than 45 markets (duplicate licenses in some markets) managed by AstraZeneca partners – Serum Institute of India (SII), R-pharm, Fiocruz, and Verity Pharmaceuticals. COVID-19 VACCINE ASTRAZENECA is distributed via COVID-19 Vaccines Global Access (COVAX), in collaboration with United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO), under a World Health Organization (WHO) Emergency Use Listing to more than 80 countries.

A summary of the worldwide marketing approval status applicable to COVID-19 VACCINE ASTRAZENECA is provided in Table 1.

Table 1 Summary of worldwide marketing authorisation status applicable to COVID-19 VACCINE ASTRAZENECA

Country	Date of Authorisation
Argentina	30 December 2020
Australia	15 February 2021
Brazil	12 March 2021
Brunei	27 May 2021
Canada	19 November 2021 (5 ml) 26 February 2021 (4 ml)
Chile	27 January 2021
Colombia	23 February 2021
Costa Rica	26 February 2021
Dominican Republic	30 December 2020
Ecuador	23 January 2021
El Salvador	30 December 2020
European Union/European Medicines Agency (includes Norway, Lichtenstein & Iceland).	29 January 2021
Great Britain	24 June 2021 (Conditional Marketing Authorisation)
Guatemala	21 June 2021
Honduras	05 February 2021

Table 1 Summary of worldwide marketing authorisation status applicable to COVID-19 VACCINE ASTRAZENECA

Country	Date of Authorisation
Hungary	21 January 2021
Indonesia	23 April 2021
Japan	21 May 2021
Korea, Republic of (South)	10 February 2021 (Domestic Supply) 21 May 2021 (Overseas Supply)
Malaysia	02 March 2021
Maldives	20 June 2021
Mexico	04 January 2021
Montenegro	05 March 2021
New Zealand	29 July 2021
Panama	05 February 2021
Peru	07 September 2021
Philippines	28 January 2021
Serbia	05 March 2021
Taiwan	20 February 2021
Thailand	20 January 2021
Ukraine	20 April 2021
United Kingdom	29 December 2020 (Regulation 174 Emergency Use Authorization)
Uruguay	11 February 2021
Vietnam	21 October 2021
World Health Organization	15 February 2021(South Korea supply) 16 April 2021 (European Union supply) 09 July 2021 (Japan supply) 09 July 2021 (Australian supply) 27 August 2021 (Canadian supply) 23 December 2021 (Mexican supply)

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

The following significant actions related to safety were taken during the reporting period:

In November 2021, AstraZeneca updated the Company CDS Section 4.4 (Warnings and precautions) to add new text regarding very rare events of cerebrovascular sinus thrombosis (CVST) to inform healthcare professionals that CVST and thrombosis with thrombocytopenia syndrome (TTS) require a different treatment approach and recommend that applicable guidance be consulted. Subsequently, AstraZeneca added CVST without thrombocytopenia as an Important potential risk in the Core risk management plan (RMP).

Also, in response to impositions received from European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA) and other health authorities local market product information documents have been updated with:

[a] A contraindication for individuals with a known history of Capillary Leak Syndrome (CLS) and information that patients with an acute episode of CLS following vaccination require prompt recognition and treatment (June 2021).

- Information for healthcare professionals to be alert of Guillain-Barré Syndrome (GBS) signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes (July 2021). In addition, due to imposition, GBS was added as an Important identified Risk in the EU RMP for COVID-19 VACCINE ASTRAZENECA.

- Information stating that if an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination (October 2021). Due to an imposition, Thrombocytopenia, including immune thrombocytopenia was added as an Important identified risk in the EU RMP for COVID-19 VACCINE ASTRAZENECA.

Following Health Authority impositions Direct Healthcare Professional Communication (DHPC) letters were disseminated providing additional information on the risk of thrombocytopenia (including immune thrombocytopenia) with or without associated bleeding (October 2021) and CLS (June 2021).

During the late-breaking period of this Periodic Safety Update Report (PSUR), AstraZeneca received impositions from EMA, MHRA, and other health authorities to update local product information regarding Transverse myelitis. Updates to the local product information are ongoing at the time of this PSUR.

4 CHANGES TO REFERENCE SAFETY INFORMATION

AstraZeneca's reference safety information is the CDS. The CDS covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product (providing the medical and scientific information AstraZeneca believes is necessary for the safe and effective use of a product); it serves as the master document for regular implementation of material changes in national or local authorised product information.

The COVID-19 VACCINE ASTRAZENECA CDS in effect at the beginning of the reporting period was dated 17 June 2021.

During this reporting period, the COVID-19 VACCINE ASTRAZENECA CDS was updated once to include the safety-related changes summarised in Table 2.

Table 2 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECAAZD1222 CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
02 November 2021	**CDS Section 4.4 - Special warnings and special precautions for use** Hypersensitivity including anaphylaxis Text has been revised to clarify that a subsequent dose should not be given to those who have experienced a severe hypersensitivity reaction to a previous dose of the vaccine.	Not applicable
	Thromboembolism and thrombocytopenia Added information that the reporting rates after the second dose are lower compared to after the first dose.	Not applicable
	Thromboembolism and thrombocytopenia Added the following new text pertaining to information that events of cerebrovascular venous and sinus thrombosis without thrombocytopenia: Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been reported very rarely following vaccination with COVID-19 Vaccine AstraZeneca, although a causal relationship has not been established. These events can be fatal and may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance.	Further information regarding this change is presented in Section 16.2.2

Table 2 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECAAZD1222 CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
02 November 2021	**CDS Section 4.8 – Undesirable effects** Summary of safety profile Added information about the observed reactogenicity in participants who received a booster dose in the COV001 study.	Not applicable

CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, TTS Thrombosis with Thrombocytopenia Syndrome

A copy of the COVID-19 VACCINE ASTRAZENECA CDS in effect at the end of the reporting period is presented in Appendix 1. For the purpose of this PBRER, this CDS (version 10.0, dated 02 November 2021), is the reference for both the benefit and risk sections.

Post data-lock, the CDS was updated with the following safety-related changes:

- On 06 January 2022, Section 4.6 (Pregnancy and lactation) was updated to reflect current safety data regarding vaccine administration in pregnancy women. The recommendation was updated to consider the use of COVID-19 VACCINE ASTRAZENECA during pregnancy when the benefits outweigh the risks
- On 17 January 2022, Section 4.6 (Pregnancy and lactation) was further updated to reflect current safety data regarding vaccine administration in lactating/breastfeeding women.
- On 04 February 2022, Section 4.4 (Special warnings and special precautions for use) and Section 4.8 (Undesirable effects) were updated to support changes to the recommendation for use of COVID-19 VACCINE ASTRAZENECA as a booster dose (third dose) after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).

In addition, during the Late Breaking period, AstraZeneca has validated signals of hypoaesthesia/paraesthesia, and GBS. CDS Section 4.8 is currently under revision to include hypoaesthesia and paraesthesia as Adverse Drug Reactions (ADRs) and this is in the late-stage of being finalized. AstraZeneca is further reviewing GBS as part of standard internal signal evaluation processes. Conclusions and any recommended actions for this signal will be communicated in the next PSUR (see section 14), or earlier as necessary.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 3, based on actual enrolment/randomisation schemes for ongoing trials.

Table 3 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
COVID-19 VACCINE ASTRAZENECA	35889[a]
AZD2816[b]	1523[a]
MenACWY	10947
Rabies vaccine	200
Placebo	11959

Cumulative numbers from initiation of the first clinical trials up to 28 December 2021. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

MenACWY Meningococcal Vaccine.

[a] Due to a programming error, estimated cumulative subject exposure for COVID-19 VACCINE ASTRAZENECA and AZD2816 were incorrectly reported in the Development Safety Update Report (review period: 26 March 2021 – 28 December 2021). These numbers have been corrected and included in Table 3 above.

[b] AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 4 and Table 5, respectively.

Table 4 Estimated cumulative subject exposure to COVID-19 VACCINE ASTRAZENECA and AZD2816 from ongoing clinical trials by age and sex

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
1-11	56	55	111
12-17	76	74	150
18-64	24873	25052	49925
>=65	5867	4366	10233
Missing	70	29	99
Total	30942	29576	60518[a]

Data from ongoing clinical trials as of 28 December 2021.

All dosed subjects are included. Gender is based on biological sex at birth in COV008 study.

[a] Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

Table 5 Estimated cumulative subject exposure to COVID-19 VACCINE ASTRAZENECA and AZD2816 from ongoing clinical trials by racial group

Racial group	Number of subjects
American Indian Or Alaska Native	1289
Asian	2593
Black Or African American	5885
Native Hawaiian Or Other Pacific Islander	81
White	46000
Other	1570
Multiple Categories Checked	1906
Missing	794
Total	60118[a]

Data from ongoing clinical trials as of 28 December 2021. All dosed subjects are included.

Other race category includes multiple race categories.

400 subjects from COV004 excluded as race was not collected in this study.

[a] 400 subjects from Study COV004 not included since racial groups were not collected in this study. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

5.2 Cumulative and interval patient exposure from marketing experience

5.2.1 Post-approval (non-clinical trials) exposure

The post-marketing patient exposure data in this report is presented by number of doses distributed and doses administered. All exposure is intended for the same indication and route of administration.

For doses distributed, this information has been provided below in section 5.2.1.1 and it includes dose distribution information across all markets, those where AstraZeneca is the Marketing Authorisation Holder and those supported by the licence partners.

For doses administered to vaccinees, this is a more accurate measure of vaccinee exposure and provides more detailed vaccinee-level data (eg, gender and age category). Therefore, AstraZeneca is continuing to work on the collection of this information at the country level, from relevant health departments, for all countries administering the COVID-19 VACCINE ASTRZENECA. However, at the time of this report, AstraZeneca has received exposure data

based on doses administered to vaccinees in specific countries/regions only; additional information can be found in section 5.2.1.2 below.

5.2.1.1 Patient exposure – doses distributed

During this reporting period, the global post-marketing patient exposure (by doses distributed) to COVID-19 VACCINE ASTRAZENECA was estimated to be over 1.8 billion doses.

The cumulative global post-marketing patient exposure (by doses distributed) to COVID-19 VACCINE ASTRAZENECA, since launch to 31 December 2021, have been estimated to be over 2.4 billion doses.

The regional dose distribution data is presented in Table 6.

Table 6 COVID-19 VACCINE ASTRAZENECA exposure, based on doses distributed, by Region

Region[b]	Exposure by doses distributed		Percentage (%)	
	Interval (26 June 2021 to 31 December 2021)	Cumulative (Up to 31 December 2021)	Interval	Cumulative
Europe	90143440	218687400	4.81	8.88
International	472376820	557239620	25.18	22.62
North America	6479000	8953500	0.35	0.36
Japan	53338170	53338170	2.84	2.16
Serum Institute of India[a]	1150920270	1466804570	61.36	59.53
Fiocruz[a]	93820400	148614150	5.00	6.03
R-Pharm[a]	8632900	10358700	0.46	0.42
Total	**1875711000**	**2463996110**	-	-

[a] Data from Serum Institute of India, Fiocruz, and R-Pharm is as of 31 December 2021.

[b] Where AstraZeneca (AZ) is the Marketing Authorisation Holder, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation.

A more detailed breakdown of doses distributed across the countries within the EU can be found in Appendix 6.

5.2.1.2 Post-marketing patient exposure data for reporting period and cumulatively

AstraZeneca has obtained exposure data based on doses administered to vaccinees in EU, UK, Australia, Philippines, India, Canada, Argentina, Bangladesh, Brazil, Chile, Guatemala,

Lebanon, Malaysia and Uruguay. This information is summarised in Table 7 below and it represents the interval and cumulative exposure (by doses administered). This data has either been provided to AstraZeneca directly from Government bodies or has been sourced from country specific websites.

Administration data from the licence partners (Serum Institute of India, Fiocruz and R-Pharm) have not been provided to AstraZeneca directly.

Please note that administration in other markets where the COVID-19 VACCINE ASTRAZENECA is authorised has not yet been made available to AstraZeneca. As such, the doses administered presented in this report is less than the doses distributed.

Table 7 COVID-19 VACCINE ASTRAZENECA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval		Cumulative		Percentage (%)	
	Dose 1	Dose 2	Dose 1	Dose 2	Interval	Cumulative
European Union	848841	13156311	39111582	29825433	1.16	4.31
United Kingdom	191097	2886613	24803571	24166444	0.26	3.07
Australia	2735660	6286798	6873833	6740025	0.75	0.85
Philippines	11569396		14192014		0.96	0.89
India	984004783		1264211249		81.29	78.94
Canada	206948		2803871		0.02	0.18
Argentina	9949751	9551025	9949751	9551025	1.62	1.22
Bangladesh	14305313	7371670	14305313	7371670	1.80	1.36
Brazil	115043755		115043755		9.53	7.20
Chile	545440		545440		0.05	0.03
Guatemala	1730474	1125665	1730474	1125665	0.24	0.18
Lebanon	688878		688878		0.06	0.04
Malaysia	2043338	2022371	2043338	2022371	0.34	0.25
New Zealand	2458		2458		0.0002	0.0002
South Korea	20443988		20443988		1.69	1.28
Uruguay	88924		88924		0.01	0.01
Grand Total	**1206799497**		**1597641072**		-	-

The data cut off for Brazil is 09 December 2021 and that of New Zealand is 14 December 2021.

The data cut off for Australia is 19 December 2021.

The data cut off for European Union, Chile, Philippines, South Korea, United Kingdom, Uruguay is 26 December 2021.

The data cut off for Bangladesh, Guatemala, India, Lebanon, Malaysia is 27 December 2021.

The data cut off for Argentina is 28 December 2021 and that of Canada is 31 December 2021.

A more detailed presentation of doses administered by country/states as well as vaccine administration by dose number, age and/or gender where provided for specified countries can be found in Appendix 6. However, a summary of the post-marketing patient exposure by age and gender (as currently available) is presented in Table 8 and Table 9, respectively.

Table 8 presents the vaccine doses administered by Age Group for the following specific countries:

- Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UK.

Table 8 Vaccine Doses Administered by Age Group

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	Percentage (%)	Dose 1	Dose 2	Total	Percentage (%)
18-24	610452	685139	1295591	2.12	1183045	1016892	2199937	1.67
25-49	8840389	9918847	18759236	30.73	14544648	13335258	27879906	21.20
50-59	396492	2306587	2703079	4.43	11255357	10549130	21804487	16.58
60-69	1125551	7835398	8960949	14.68	16616682	15990122	32606804	24.79
70-79	823546	4634537	5458083	8.94	9928707	9718097	19646804	14.94
≥80	117619	221350	338969	0.56	1964022	1884253	3848275	2.93
Unknown	15288260	8234568	23522828	38.54	15296525	8238500	23535025	17.89
Total	**27202309**	**33836426**	**61038735**	**100**	**70788986**	**60732252**	**131521238**	**100**

The total doses administered by Age group do not reflect the total doses administered that appear in Table 7. This is due to the fact that doses administered by Age group are not available for all countries that have provided vaccine administration information.

There was an error noted in Table 7 (COVID-19 VACCINE ASTRAZENECA cumulative exposure based on doses administered by age group from 29 December 2020 through 27 June 2021) of the previous PSUR in which the column totals for Dose 1, Dose 2 and Total were incorrectly summed. The corrected cumulative number of doses administered through 27 June are as follows: Dose 1 – 50241492 doses, Dose 2 – 32747804 doses, and Total – 84835699 doses. Administration data from this table was not used in the observed vs. expected calculations. Therefore, this error has no impact on the observed vs. expected analyses reported in the previous PSUR.

Table 9 present the vaccine doses administered by Gender Group for the following specific countries:

- Australia and UK

Table 9 Vaccine Doses Administered by Gender Group

Gender group	Total doses administered		Percentage (%)	
	Interval	Cumulative	Interval	Cumulative
Male	7066298	30689698	51	49
Female	6735643	31695778	49	50.5
Unspecified	14343	198397	0	0.3
Total	**13816284**	**62767927**	**100**	**100**

The total doses administered by Gender group does not reflect the total doses administered that appears in Table 7. This is due to the fact that doses administered by Gender group is not available for all countries that have provided vaccine administration information.

Exposure by doses administered is used as part of Observed versus Expected (O/E) Analyses, refer to Appendix 8 for further details.

AstraZeneca will continue efforts to obtain exposure data by gender for each EU Member State, as currently the data provided via the European Centre for Disease Prevention and Control does not include gender breakdown at a country level. If this data become available, it will be included in future reports.

5.2.2 Post-approval use in special populations

It is not possible to provide an estimate of patient numbers exposed from post-approval use in special populations.

5.2.3 Other post-approval use

AstraZeneca is not aware of any patterns of use (for example overdose, drug abuse, misuse or off-label use) of COVID-19 VACCINE ASTRAZENECA considered to be relevant for the interpretation of safety data.

6 DATA IN SUMMARY TABULATIONS

6.1 Reference information

The Medical Dictionary for Regulatory Activities (MedDRA), version 24.1, has been used for coding adverse events (AEs). The summary tabulations are arranged in the internationally

agreed order by primary MedDRA System Organ Class (SOC), and refer to the Preferred Term (PT) level.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca and University of Oxford sponsored interventional clinical trials that have been reported during the COVID-19 VACCINE ASTRAZENECA clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (DLP) 28 December 2021 organised by SOC, is presented in Appendix 2.

A summary of the total number of case reports with SAEs from AZD1222 (COVID-19 VACCINE ASTRAZENECA) clinical trials along with the total number of SAEs for each treatment is provided in Table 10.

Table 10 Summary tabulation of serious adverse event case reports received from AZD1222 (COVID-19 VACCINE ASTRAZENECA) clinical trials[a]

Treatment	Interval (29 June 2021 – 28 December 2021)		Cumulative (through 28 December 2021)	
	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Adverse Events
AZD1222	672	765	1429	1591
AZD2816[c]	13	14	13	14
MENACWY	244	262	669	714
Meningocccal Group B Vaccine	3	4	4	5
Placebo	415	489	742	857
Study procedure	2	2	4	4
Total[b]	**677**	**771**	**1438**	**1601**

[a] Numbers presented in this table will not match those presented in Appendix 2 due to differences in the date that the table and appendices were generated from the AstraZeneca global safety database.

[b] Cases may have more than one treatment listed. Therefore, the sum of cases and SAEs will exceed the total.

[c] AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

A review of Table 1 of Appendix 2 has been completed for the PBRER period from 29 June 2021 to 28 December 2021 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRER.

6.3 Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "a reasonable possibility of a causal relationship between the medicinal product and the event" for Table 2 Appendix 2) that have been reported from marketed experience with COVID-19 VACCINE ASTRAZENECA, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2.

A summary of the total number of COVID-19 VACCINE ASTRAZENECA case reports and corresponding adverse events received from Spontaneous sources by seriousness for both the interval and cumulative periods is provided in Table 11.

Table 11 Summary tabulation of COVID-19 VACCINE ASTRAZENECA case reports and adverse events received from spontaneous sources[a]

Case/Event Seriousness	Interval (29 June 2021 – 28 December 2021)		Cumulative (through 28 December 2021)	
	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events
Serious	53971	171497	222567	864258
Non-Serious	152331	551958	420706	1556750
Not available/ Not entered	1	0	8	26
Total	206303	723455	643281	2421034

[a] Numbers presented in this table will not match those presented in Appendix 2 due to differences in the date that the table and appendices were generated from the AstraZeneca global safety database.

A review of Table 2 Appendix 2 has been completed for the PBRER period from 29 June 2021 to 28 December 2021. The increase in the absolute frequency numbers from the previous PBRER observed in Table 2 Appendix 2 as for many of the reporting intervals included in section 15 and section 16 of this PSUR is likely due to the ongoing COVID-19 mass-vaccination campaign and is not indicative of a safety concern.

6.3.1 Fatal events, including case reports involving Preferred Term (PT) of Sudden Death

6.3.1.1 Fatal Events

Interval Review (29 June 2021 – 28 December 2021)

During the reporting period (29 June 2021 to 28 December 2021), 2609 cases with fatal outcomes were received.

The age of the vaccinees was reported in 2272 cases (87%) and was unknown in 337 cases (13%). In 1077 (47%) of the 2272 case reports, the vaccinees were aged 65 years and above, out of which 351 vaccinees were aged 80 years and above. The median age of the vaccinees in the fatal cases was 64 years. The gender distribution as reported in 2482 cases (95%) was 1108 females (45%) and 1374 males (55%).

Sufficient case information regarding comorbid conditions was available only in 873 cases (33%). Important comorbid conditions identified in decreasing order of frequency included hypertension (n=272); cardiac conditions (ie, coronary artery disease, cardiomyopathy, atrial fibrillation, etc) (n=202); diabetes (n=176); chronic respiratory conditions (such as chronic obstructive pulmonary disease, asthma, interstitial lung disease, etc) (n=121); vascular pathologies (ie, arteriosclerosis, cerebrovascular disease, aneurysms, deep vein thrombosis, etc) and coagulation or bleeding disorders (n=116).

Out of 2609 cases there was insufficient information to characterize the cause of death in 772 of the fatal case reports (29.6%). The most relevant causes of death in the remaining 1837 fatal case reports (70.4%) received during the reporting interval are presented in Table 12 below:

Table 12 Distribution of the most relevant Causes of Death determined from reported fatal events in Fatal Cases with COVID- 19 VACCINE ASTRAZENECA where Cause of Death was Reported (n = 1837) as per cause of death (Interval period: 29 June 2021 – 28 December 2021)

Cause of Death	Fatal cases [a]
Cardiorespiratory causes	695
Infection [b]	291
Cerebrovascular accident without reported thrombocytopenia	151
Thrombosis without thrombocytopenia	131
Thrombosis with Thrombocytopenia (including cerebral venous sinus thrombosis (CVST)) (including Cerebral venous thrombosis (CVT)) (including Cerebral venous thrombosis (CVST and CVT)) (including deep vein thrombosis) (including pulmonary embolism) (including intraabdominal thrombosis)	102 (49) (20) (3) (15) (9) (6)
Cerebral haemorrhage	92
Thrombocytopenia	42
Gastrointestinal causes	35
Seizure	35
Renal dysfunction	33
Multiple organ failure	33
Malignancy	31
Thrombocytopenia with haemorrhage	28
CVST without thrombocytopenia	19
Aneurysm	18
Anaphylaxis/ Hypersensitivity	19
Hepatitis	11
Guillain Barre Syndrome	10
CVT without thrombocytopenia	5
Pancreatitis	4
Haemophagocytic lymphohistiocytosis	3
Vasculitis	3
Others	177
Total	**1837**

[a] In some cases, single most relevant cause of death could not be determined due to insufficient information.
[b] Causes of infection include COVID-19 and other causes, such as bronchitis, pneumonia, meningitis.

CVST Cerebral Venous Sinus Thrombosis; CVT Cerebral Venous Thrombosis

Of the 291 case reports where Infections were reported as the cause of death, 180 cases (62%) reported COVID-19 infection as the cause of death. Out of 180 cases, 131 cases (72.8%) were reported with first dose of vaccine and time to death or fatal outcome ranged from 5 days of vaccination to 203 days. The remaining 49 fatal reports of COVID-19 infection were reported after the second dose of vaccination and the time to fatal outcome ranged from 9 days to 213 days. Other infections reported included: sepsis, pneumonia, lower respiratory tract infection, meningitis, bacterial bronchitis, gastroenteritis, osteomyelitis, infective bronchiectasis, pneumocystis carinii, mucormycosis, and community acquired pneumonia.

Out of the 2609 case reports with fatal outcome, 1522 were medically confirmed (58%). Of the 2609 cases, 79 (3.02%) were reported as Sudden Death. Case reports of Sudden Death are included in the overall number of cases with fatal outcome. During the reporting period one fatal case (PPD) was reported with booster dose, however there was insufficient information on dates of vaccination and cause of death (the only reported PT was 'Death').

Table 13 presents an overview of fatal cases per age group during the reporting period.

Table 13 Fatal cases per age group (in years)

Age group	Fatal cases
< 18	2[a]
18-49	478
50-59	350
60-64	365
65-74	536
≥ 75	541
Unknown	337
Total	**2609**

[a] Comprising Insufficient case details received from regulatory source (Vaccination dates, off label use, medical history, autopsy). 2 cases - ages are PPD and PPD years old.

An O/E analyses for fatal cases was completed and the results of the O/E analyses are presented in Table 14, Table 15 and Table 16. References for background estimates obtained from the literature are provided in Appendix 9.

Table 14 Observed versus expected analyses for Fatal cases by age group in EEA

Medical Concept	Age Group	Risk window in days	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
Fatal Reports [a] (from EEA)	18 - 49	42	109	872.11	0.12 (0.1 - 0.14)	Observed significantly < expected
	50 - 59	42	108	1394.3	0.08 (0.06 - 0.09)	Observed significantly < expected
	60 - 69	42	362	6764.24	0.05 (0.05 - 0.06)	Observed significantly < expected
	70 - 79	42	254	5095.84	0.05 (0.04 - 0.06)	Observed significantly < expected
	>80	42	171	2061.03	0.08 (0.07 - 0.1)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from EU, as corresponding exposure was only available from this region.
[b] Includes cases reported within risk window of 42 days.
CI Confidence Interval; EEA European Economic Area.

Table 15 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
Fatal Reports [a] (from UK)	18 - 29	42	23	75.48	0.3 (0.19 - 0.46)	Observed significantly < expected
	30 - 39	42	30	206.48	0.15 (0.09 - 0.2)	Observed significantly < expected
	40 - 49	42	52	1182.46	0.04 (0.03 - 0.06)	Observed significantly < expected
	50 - 59	42	103	2949.56	0.03 (0.03 - 0.04)	Observed significantly < expected

Table 15 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
	60 - 69	42	123	3557.19	0.03 (0.03 - 0.04)	Observed significantly < expected
	70 - 79	42	180	4316.74	0.04 (0.04 - 0.05)	Observed significantly < expected
	>80	42	242	5207.18	0.05 (0.04 - 0.05)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from UK, as corresponding exposure was only available from this region.
[b] Includes cases reported within risk window of 42 days.
CI Confidence Interval; UK United Kingdom.

Table 16 Observed versus expected analyses for Fatal cases overall

Medical Concept	Observed cases	Expected cases	Risk Window	Background rate/100,000 person years	Rate ratio (CI 95%)	
Fatal Reports [a]	3053	122,653.51	42	365.75	0.02 (0.02 - 0.02)	Observed significantly < expected
Fatal Reports RW42+Unknown TTO [a]	4601	122,653.51	42	365.75	0.04 (0.03 - 0.04)	Observed significantly < expected

[a] Includes global reports irrespective of age and gender.
CI Confidence Interval, RW Risk Window, TTO Time to onset.

The observed versus expected analysis of fatal reports showed that observed cases occurred significantly less frequently than expected for all ages and by different age stratifications from European Economic Area (EEA) and UK.

Cumulative Review (29 December 2020 – 28 December 2021)

Cumulatively through 28 December 2021, there have been 4992 valid fatal cases reported. An additional 106 cases did not fulfil the criteria for a valid case such as identifiable patient or identifiable reporter while two cases were suppressed due to having duplicate case information. Out of 4992 cases, age of the vaccinees was reported in 4203 cases (84%) and age was unknown in 789 cases. In 2302 (55%) of the 4203 case reports, the vaccinees were

aged 65 years and above, out of which 773 vaccinees were aged 80 years and above. The median age of the vaccinees in the fatal cases was 66 years. The gender distribution as reported in 4792 cases (95%) was 2177 females (44%) and 2615 males (56%).

Cumulatively out of the 4992 case reports with fatal outcome 2889 (58%) were medically confirmed. Of the 4992 cases, 221 (4.4%) were reported as Sudden Death. Case reports of Sudden Death are included in the overall number of cases with fatal outcome.

6.3.1.2 Events with PT of Sudden Death

Interval Period (29 June 2021 – 28 December 2021)

During the reporting period, out of 79 cases, 67 cases (85%) containing the PT of Sudden death and 12 cases (15%) containing the PT of Sudden cardiac death were reported.

Of the 79 case reports, 53 were medically confirmed (67%). Forty-eight (48) vaccinees were male (62%), 29 were female (38%), and in 2 reports gender was unknown. Age of vaccinees of the sudden death cases ranged from 19 to 88 years with a median age of 63.5 years. The medical history (vaccinees may have had >1 comorbidity) included hypertension, cardiac failure, coronary artery disease, myocardial infarction, diabetes mellitus, renal failure, chronic obstructive pulmonary disease (COPD), dementia, epilepsy, hypothyroid, renal cancer, fall and cerebral palsy. The medical history was not reported in 41 cases (52%).

There were 25 cases where time to death ranged from 0 to 96 days after receiving the first dose of the vaccine, there were 11 cases where time to death was 0 to 73 days after receiving the second dose and here were 43 cases where time to death ranged from 0 to 168 days after receiving the unknown dose of the vaccine. During the reporting period there were 12 sudden deaths with a risk window of 7 days.

Of the 79 cases of sudden death, cause of death was provided in 29 cases and included the PTs of: Cardiac arrest, Myocardial ischaemia, Pneumonia, Pulmonary embolism, pulmonary oedema, Asthenia, Hyperpyrexia, Cardio-respiratory arrest, Chest pain, Aortic dissection, Deep vein thrombosis, Aneurysm ruptured, Cardiomegaly, Myocardial infarction, Multiple organ dysfunction syndrome, Cardiovascular disorder, Respiratory arrest, Hypertension, Dyspnoea, Cardiac failure chronic, Coronary artery occlusion, and Circulatory collapse.

Cumulative Review (29 December 2020 – 28 December 2021)

Cumulatively of the 221 case reports with Sudden death outcome, 166 (75%) were medically confirmed. One thirty one (131) vaccinees were male (60%), 87 were female (40%), and in 3 reports gender was unknown. Age of vaccinees in the sudden death cases ranged from 19 to 97 years with a median age of 66 years. The medical history (vaccinees may have had >1 comorbidity) included chronic obstructive pulmonary disease (COPD), hypertension,

diabetes mellitus, schizophrenia, alcoholic cirrhosis, arterial occlusive disease, cardiac disorder, cardiac failure, myocardial infarction, dyslipidaemia, osteoarthritis, gastroesophageal reflux disease, Parkinson's disease, multiple sclerosis, obesity, renal failure, heart failure, frailty, dementia, hepatitis, epilepsy, hypothyroidism, polycythaemia vera, cancer, alcohol abuse, tobacco use, and transient ischemic attack, epilepsy, hypothyroid, renal cancer, fall and cerebral palsy. The medical history was not reported in 78 cases (35%).

There were 73 cases where time to death ranged from 0 to 96 days after receiving the first dose of the vaccine, there were 16 cases where time to death was 0 to 73 days after receiving the second dose and there were 132 cases where time to death ranged from 0 to 168 days after receiving the unknown dose of the vaccine. Cumulatively there were 108 cases of sudden deaths with a risk window of 7 days.

Of the 221 cases of sudden death, cause of death was provided in 85 cases and included the PTs of: Cardiac arrest, Myocardial ischaemia, Myocardial infarction, Left ventricular dysfunction, Atrial fibrillation, Pneumonia, Pulmonary embolism, Pulmonary oedema, Asthenia, Hyperpyrexia, Arthralgia, Cardio-Respiratory arrest, Chest pain, Aortic dissection, Deep vein thrombosis, Subarachnoid haemorrhage, Aneurysm ruptured, Contusion, Cardiomegaly, Multiple organ dysfunction syndrome, Acute coronary syndrome, Cardiovascular disorder, Visceral venous thrombosis, Cor pulmonale acute, Respiratory arrest, Hypertension, Haemorrhage intracranial, Dyspnoea, Cardiac fibrillation, Cerebral infarction, Gastrointestinal haemorrhage, Cerebrovascular accident, Cardiac failure chronic, Coronary artery occlusion, Sudden unexplained death in epilepsy and Circulatory collapse.

This review of cases of all fatal case reports and a specific review of Sudden death, along with the O/E analysis of fatal cases (all fatal and by age group [Table 14]) and Sudden death (Appendix 8) did not indicate any new safety concern with COVID-19 VACCINE ASTRAZENECA.

6.3.2 Post-marketing reports of Lack of efficacy

Interval Period (29 June 2021 – 28 December 2021)

A search of the global safety database for the reporting interval using the Lack of Efficacy standardised MedDRA query (SMQ), retrieved 5194 reports with the following 5210 PTs: Vaccination failure (4750), Drug ineffective (401), Therapeutic product ineffective (15), Treatment failure (13), Therapy non-responder (6), Therapeutic product effect decreased (5), Therapeutic product effect incomplete (4), Disease progression (3), Drug effect less than expected (3), Therapeutic response decreased (3), Absence of immediate treatment response (2), Drug tolerance increased (1), Drug level decreased (1), Therapeutic response changed (1), Therapeutic response shortened (1), and Therapeutic response delayed (1).

Of the 5194 reports, 4773 (91.9%) were medically confirmed and the remaining 421 (8.1%) were consumer reports. A total of 4521 (87.0%) reports were considered serious due to the AE being considered medially important (4201), the AE was reported to have resulted in disability (9), required hospitalization (342), was life threatening (57), and/or resulted in death (47). Cases may have met more than one criteria for seriousness. The remaining 673 (13.0%) reports were non-serious. There were 47 fatal cases in the reporting interval (see case IDs PPD

below).

Of the 5147 non-fatal cases, the outcomes were as follows:

Not recovered (263), Recovered (453), Recovered with sequelae (2), Recovering (261), and Unknown (4168).

Information on COVID-19 test was available in 3132 reports; of these 3104 (99.1%) were reported as COVID-19 test positive and 19 (0.6%) were reported as COVID-19 test negative and 9 (0.3%) were reported as unknown. Information on the 3104 reports (194 with first dose and 2910 with second dose) with a positive COVID-19 test is presented below:

- In 194 (6.2%) of the 3132 reports, COVID-19 test was positive after the receipt of the first dose of the vaccine; time to positive COVID-19 test was available for 108 (55.7%) cases and ranged from the same day as vaccination to 271 days with a median of 107 days. In 4 (2.1%) reports, the date of the positive test result was before the first dose vaccination date. In 82 (42.3%) reports, time to positive Covid-19 test after first dose of vaccine was unknown.

- In 2910 (92.9%) reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; time to positive COVID-19 test was available for 2866 (98.5%) cases and ranged from 0 days to 265 days with a median of 100 days. In 44 (1.5%) reports, time to positive COVID-19 test after second dose of vaccine was unknown.

Cumulative Review (29 December 2020 – 28 December 2021)

A cumulative search of the global safety database using the Lack of Efficacy SMQ, retrieved 5844 reports with the following 5866 PTs: Vaccination failure (4821), Drug ineffective (933),

Therapeutic product ineffective (33), Treatment failure (21), Disease progression (10), Therapeutic product effect decreased (10), Therapy non-responder (8), Therapeutic product effect incomplete (6), Therapeutic response decreased (4), Drug effect less than expected (3), Absence of immediate treatment response (2), Therapeutic response shortened (2), Paradoxical drug reaction (2), Therapeutic product effect delayed (2), Drug level decreased (2), Drug tolerance increased (1), Therapeutic reaction time decreased (1), Diet failure (1), Remission not achieved (1), Therapeutic response changed (1), Therapeutic response delayed (1), Device defective (1).

Of the 5844 reports, 4962 (84.9%) were medically confirmed and the remaining 882 (15.1%) were consumer reports. A total of 4755 (81.4%) reports were considered serious due to the AE being considered as medically important (4382), the AE was reported to have resulted in disability (21), required hospitalization (395), was life threatening (68), and/or resulted in death (60). Cases may have met more than one criteria for seriousness. The remaining 1089 (18.6%) reports were non-serious. There were 60 fatal cases in the reporting interval as detailed below.

- PPD : Case from PPD where a PPD-year-old patient (gender unknown) with an unknown medical history, experienced pneumonia after vaccination. The patient experienced positive covid test and lack of efficacy. The patient died due to pneumonia on an unspecified date. It is not known whether an autopsy was performed. Vaccination dates and time to onset are unknown.

- PPD : Case reported multiple patients (age, gender and medical history unknown) who experienced respiratory failure, SARS CoV 2, positive real-time polymerase chain reaction (RT-PCR), fever and lack of efficacy post vaccination. The patients died on an unspecified date. It is not known whether an autopsy was performed. Vaccination dates and time to onset are unknown.

- PPD : Case where a PPD-year-old PPD patient with a medical history of PPD , experienced SARS-CoV-2 positive and lack of efficacy 7 days after vaccination and died 3 days later on PPD . It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history, experienced lack of effect and COVID-19 symptoms 1 day after vaccination. On an unspecified date the patient died due to hemispheric stroke and COVID-19 symptoms. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history experienced acute coronary syndrome, tachycardia, malaise, chest pain, and dyspnoea 2 days after vaccination. On an unspecified date the patient

experienced suspected COVID-19 infection and lack of efficacy. The patient died on an unspecified date. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD patient of unknown age with medical history of PPD , experienced COVID-19 pneumonia and vaccination failure on an unspecified date after vaccination. The patient tested positive for SARS CoV-2 test 8 days after vaccination. The patient experienced cerebral artery occlusion and a further positive Sars-Cov-2 test 14 days post vaccination. The patient died on PPD due to stroke, cerebral vascular occlusion, COVID-19 pneumonia, vaccination failure. It is not known whether an autopsy was performed.

- PPD : Case where a patient of unknown age, gender and medical history died in PPD , approximately 3 months after receiving the second doses of the vaccination. The cause of death was unknown. It is not known whether an autopsy was performed.

- PPD : Case where a PPD -year-old PPD patient with unknown medical history, died due to worsening of COVID-19 and lack of effect approximately 2 months after vaccination. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD -year-old PPD experienced vaccination failure and COVID-19 pneumonia approximately 10 days post receiving the second dose of the vaccine. The patient was hospitalised as PPD oxygen levels started dipping and was put on a ventilator. On PPD the patient died due to COVID-19 pneumonia. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD patient of unknown age and medical history experienced COVID-19 infection and vaccination failure 77 days after the first dose and 49 days after the second dose. The patient's health worsened and PPD was put on a ventilator. The patient died on PPD . Autopsy details were unknown.

- PPD : Case from PPD where a PPD -year-old PPD patient with a history of PPD , experienced lack of efficacy and COVID-19 42 days after vaccination. The patient died from the events on PPD . An autopsy was not performed.

- PPD : Case from PPD where a PPD -year-old PPD patient with an unknown medical history, was found deceased PPD on PPD after vaccination on an unspecified date. The patient's General Practitioner (GP) attributed

PPD death to PPD underlying conditions. Cause of death was reported as disease progression. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with an unknown medical history, experienced lack of effect after vaccination with dose 1 and 2 of unknown COVID-19 vaccine. The patient died from the event on an unspecified date in PPD. An autopsy was not performed. Limited information is available for this case, including any information regarding COVID-19 testing.

- PPD : Case where a PPD-year-old PPD patient with unknown medical history, experienced lack of effect after receiving the second dose. Two (2) days post vaccination, the patient experienced fatigue, and headache. On PPD the patient tested positive for COVID-19. On an unspecified date the patient experienced severe lung complications and died due to the events. It is not known whether an autopsy was performed.

- PPD : Case from the PPD where a patient of unknown age and gender and a medical history of PPD, experienced COVID-19 infection and vaccination failure 181 days after receiving the first dose and 102 days after receiving the second dose. The patient died from COVID-19 on PPD. It is not known whether an autopsy was performed.

- PPD : Case concerns a PPD-year-old PPD patient with unknown medical history, experienced COVID-19 infection, lack of efficacy and respiratory failure 90 days after receiving the first dose (Lot MTQ187) and 28 days after receiving the second dose (Lot NFQ129). The patient remained at PPD receiving supplemental oxygen. The patient PPD and died due to respiratory failure on PPD. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a medical history of PPD, died due to SARS-CoV2 infection on an unspecified date after receiving the second dose of the vaccine. The patient experienced COVID-19, drug ineffective, fatigue, dyspnoea, asthenia, positive SARS-CoV2 RT-PCR test and oxygen saturation decreased. It is not known whether an autopsy was performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a medical history of PPD, died due to disease progression (PPD cancer stage IV and bone metastasis) 7 days after receiving the vaccination. The patient also experienced thrombosis, blood urine, device occlusion and vomiting. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD -year-old PPD patient with a medical history of PPD experienced SARS- CoV-2 infection 24 days after receiving the second dose. On an unknown date, the vaccinee also experienced blood clots and vaccination failure. On PPD the patient died from the event of SARS- CoV-2 infection. At the time of reporting the event of blood clots was improving and the outcome of the event drug ineffective was unknown. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD -year-old PPD patient with a history of PPD died 148 days after receiving the first vaccination. The date of the second vaccination was unknown. The patient died due to fatal SARS- CoV-2 pneumonia and vaccine failure. An autopsy was not performed.

- PPD : Case from PPD where a PPD -year-old PPD patient with a history of PPD experienced COVID-19 pneumonia, vaccination failure and mesenteric ischaemia 102 days after receiving the first dose and 18 days after receiving the second dose of the vaccine. The patient died on PPD due to mesenteric ischaemia. It is not known if an autopsy was performed.

- PPD : Case from PPD , where a PPD -year-old PPD patient with a history of PPD was reported to have experienced vaccination failure 45 days after receiving COVID-19 VACCINE ASTRAZENECA the vaccine. The patient died 59 days after receiving COVID-19 vaccine due to cardiocirculatory stop on PPD . An autopsy was not performed.

- PPD : Case from PPD where a PPD -year-old PPD patient with a history of PPD was reported to have died 107 days after the first dose and 29 days after the second dose of the vaccination due to SARS- CoV-2 pneumonia and vaccine failure. It was unknown if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD died after reportedly experiencing vaccination failure on an unknown date after the second vaccination. It was unknown if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD died 82 days after receiving the vaccination. Death was reported due to vaccination failure and COVID-19 pneumonitis. An autopsy was not performed.

- PPD : A literature report from PPD where PPD-year-old PPD patient with a comorbidity of PPD died 20 days after receiving the second vaccination. The patient had received PPD kidney transplant PPD years before COVID-19 vaccine with no induction or anti-rejection therapy given. The patient was SARS-CoV2 positive with clinical symptoms of fever and cough for 8 days and breathing difficulty for 5 days. It was unknown if an autopsy was performed.

- PPD : Case from PPD where PPD-year-old PPD patient with a history of PPD was reported to have died from the event of ineffectiveness of the covid-19 vaccine. The patient tested positive for SARS-CoV2 PCR test post vaccination. It is not known whether autopsy was performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a medical history of PPD died 163 days post the first dose and 79 days post second dose. The patient was reported to have died from the lack of effect from both doses of the vaccine with COVID-19 pneumonitis and respiratory failure. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old male patient with a history of PPD died 125 days after the first dose and 61 days after receiving the second dose of the vaccine. The patient was reported to have died from COVID-19 pneumonitis, respiratory failure, and drug ineffective. An autopsy was not performed.

- PPD : Case reports a patient who died on an unknown date post receiving the vaccine. The patient reported lack of effect of the vaccine seen in other people. The cause of death was not reported and it was not known if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD with a history of PPD died 211 days after the first dose and 105 days after the second dose of the vaccination. An autopsy was not performed. The cause of death was reported as vaccine failure.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD died 81 days after receiving the vaccine. The patient experienced COVID-19 pneumonia and was reported to have died 64 days after receiving COVID-19 VACCINE ASTRAZENECA. The report also included the adverse event of Drug ineffective. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history, died 172 days after receiving the first dose and 88 days after the second dose of the vaccine reported as due to vaccination failure and SARS-CoV-2 infection. It was unknown if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD died 116 days after vaccination. The patient was reported to have experienced vaccination failure 98 days after vaccination and the cause of death was COVID-19 pneumonitis-ARDS on pneumopathy A COVID-19. It was unknown if an autopsy was performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a history of PPD, experienced SARS-CoV-2 infection 209 days after receiving the first dose, and 139 days after the second dose. The patient died on PPD due to severe disease from COVID-19 and reported lack of effect. The patient was intubated in the hospital. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD, experienced COVID-19 pneumonitis and reported vaccine failure 36 days after vaccination. The patient died on PPD. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD was reported to have experienced vaccination failure 103 days

after vaccination. The patient died from the event on an unspecified date. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history, was reported to have experienced SARS-CoV-2 infection and vaccination failure 159 days after the first dose and 90 days after receiving the second dose. A COVID-19 PCR test on PPD was positive. The patient died on an unspecified date from the SARS-CoV-2 infection. It is not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD , was reported to have experienced COVID-19 and vaccination failure 159 days after receiving the first dose and 100 days after the second dose. A SARS-CoV-2 PCR test on PPD was positive. The patient died on PPD . It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history was reported to have experienced vaccine failure on an unknown date after vaccination. The patient died on an unspecified date. It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with unknown medical history was reported to have experienced COVID-19 infection, vaccination failure, SARS-COV-2 PCR test positive 215 days after receiving the first dose and 159 days after receiving the second dose. The patient died on PPD . It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD patient of unknown age with a history of PPD , was reported to have died as a result of COVID-19 infection 251 days after receiving the first dose and 221 days after receiving the second dose. The patient presented to the hospital with severe breathlessness, dyspnoea on exertion, cough, fever, chills, and throat pain. RT-PCR test on PPD confirmed a COVID-19 infection. The patient was intubated and was put on mechanical ventilation on PPD . The patient died on PPD . An autopsy on an unknown date confirmed COVID-19 infection.

- PPD : Case from PPD where a PPD-year-old PPD patient was reported to have died as a result of SARS-COV-2 infection due to vaccination failure. It was not known if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD was reported to have died as a result of vaccination failure and COVID-19 pneumonia 189 days after receiving the first dose and 105 days after receiving the second dose. An autopsy was not performed. The cause of death was broncho pneumopathy with SARS-COV-2.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD was reported to have died as a result of covid lung disease, COVID-19 pneumonia, vaccination failure 192 days after receiving first dose and 108 days after receiving the second dose. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD, was reported to have experienced vaccination failure 169 days after receiving the first dose and 86 days after receiving the second dose. The patient experienced PPD and died on an unspecified date. It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD was reported to have died due to pneumonia, dyspnoea, acute respiratory insufficiency, and vaccination failure 123 days after receiving the first dose and 52 days after receiving the second dose. The patient experienced general malaise, headache, cough, arthralgia, vaccine enhanced disease, and fever. A thorax X-ray showed bilateral interstitial infiltrate. A COVID-19 antigen test and COVID-19 PCR test were both positive. It was not known if an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD, was reported to have died due to vaccination failure and COVID-19 infection 76 days after receiving the second dose. An autopsy was not performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a history of PPD, was reported to have died due to vaccination failure and COVID-19 infection 144 days after receiving the second dose. It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD, was reported to have died due to vaccination failure and COVID-19 infection 174 days after receiving the second

dose. The patient also experienced respiratory failure, cough, and dyspnoea. A RT-PCR test was positive for COVID-19 An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD , was reported to have died from COVID-19 infection, respiratory failure, and vaccination failure on an unspecified date after receiving the second dose. A RT-PCR test was positive for COVID-19. It was not known whether an autopsy was performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a history of PPD , was reported to have died due to COVID-19 infection after vaccination 140 days after receiving the second dose. A RT-PCR test was positive for COVID-19, and a thoracic-CT showed pulmonary parenchyma impairment. The patient experienced acute hypoxemic respiratory failure. It was not known whether an autopsy was performed.PPD : Case from PPD where a PPD-year-old PPD patient with a history of PPD , died due to vaccination failure and COVID-19 respiratory infection 208 days after receiving the first dose and 131 days after receiving the second dose. It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a medical history of PPD was reported to have died due to vaccination failure and COVID-19 infection 226 days after receiving the first dose and 160 days after receiving the second dose of the vaccine. It was not known whether an autopsy was performed.

- PPD : Case from PPD where an PPD-year-old PPD patient with a medical history of PPD , was reported to have experienced vaccination failure and COVID-19 infection 213 days after receiving the first dose and 129 days after receiving the second dose of the vaccine. The patient died on an unspecified date due to the events. It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with medical history of PPD , was reported to have died due to COVID-19 pneumopathy and vaccination failure, 246 days after receiving the first dose and 162 days after receiving the second dose of the vaccine. It was not known whether an autopsy was performed.

- PPD : Case report from PPD where a PPD-year-old PPD patient who was a PPD, died due to ischaemic stroke and cerebral thrombosis approximately 6 months after receiving the first dose and 4 months after receiving the second dose of the vaccine. The patient was reported to have experienced vaccination failure and COVID-19 breakthrough infection. An autopsy was not performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with a medical history of PPD was reported to have died due to vaccination failure and COVID-19 infection 253 days after receiving the first dose and 197 days after receiving the second dose for the vaccine. The patient was reported to have received treatment with Comirnaty 30 Micrograms/dose Dispersion For Injection Covid-19 Mrna Vaccine (nucleoside Modified) (tozinameran). It was not known whether an autopsy was performed.

- PPD : Case from PPD where a PPD-year-old PPD patient with medical history of PPD, experienced vaccination failure 23 days after receiving the vaccine. The patient was reported to have died of an unknown cause on an unspecified date.

- PPD : Case from PPD where a PPD-year-old PPD patient with medical history of PPD, was reported to have died due to vaccination failure and COVID-19 infection 228 days after receiving the first dose and 144 days after receiving the second dose of the vaccine. It was not known whether an autopsy was performed.

Of the 5784 non-fatal cases, the outcomes were as follows:

Not recovered (432) Recovered (611), Recovered with sequelae (4), Recovering (329), and Unknown (4408).

Information on COVID-19 test was available in 3311 reports; of these 3215 (97.1%) were reported as COVID-19 test positive and 87 (2.6%) were reported as COVID-19 test negative and 9 (0.3%) were reported as unknown. Information on the 3215 reports (295 with first dose and 2920 with second dose) with a positive COVID-19 test is presented below:

- In 295 (9.2%) of the 3215 reports, COVID-19 test was positive after the receipt of the first dose of the vaccine; time to positive COVID-19 test was available for 169 (57.3%) cases and ranged from the same day as vaccination to 271 days with a median of 59 days. In 11 (3.7%) reports, the date of the positive test result was before the first

dose vaccination date. In 115 (39.0%) reports, time to positive COVID-19 test after first dose of vaccine was unknown.

- In 2920 (90.8%) reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; time to positive COVID-19 test was available for 2875 (98.5%) cases and ranged from 0 days to 265 days with a median of 100 days. In 45 (1.5%) reports, time to positive COVID-19 test after second dose of vaccine was unknown.

Review of all the AEs associated with the lack of efficacy reports did not demonstrate any safety pattern associated with COVID-19 VACCINE ASTRAZENECA. Likewise, no new relevant safety concerns were identified during the reporting period. The imbalance of reporting rates during the reporting period and cumulatively is noted. The majority of the mass-vaccination campaigns took place during this reporting interval. The emergence of the Delta and Omicron variants during this review period may have also been a factor, but this cannot be confirmed as the reports rarely contain variant information.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

7.1 Completed clinical trials

A ‘completed’ study is defined as a study for which a final clinical study report is available (published).

No clinical trials have completed during the reporting period.

7.2 Ongoing clinical trials

There were 11 (COV001, COV002, COV003, COV004, COV005, COV006, COV008, COV009, D8110C00001, D8111C00002 and D7220C00001) ongoing clinical trials during the reporting period. For the D8110C00001 study as well as COV001, COV002, COV003 and COV005 studies enrolment had completed at the time of the primary analyses.

One trial (D8111C00001, Russia) was cancelled during the reporting period upon Sponsor decision on changes in the clinical development plan. No participants were enrolled in this Study.

There was no clinically important information that arose from ongoing clinical trials during the reporting period.

7.2.1 Ongoing Clinical Trials – Study design and results obtained on safety and efficacy

This section will report results obtained from 6 (COV001, COV002, COV003, COV005, D8110C00001 and D8111C00002) out of the 11 ongoing trials that are in scope for this report. Data analyses were not completed for the remaining 5 ongoing clinical trials.

COV001 (A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers): Phase I/II.

COV001 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase I/II trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (COVID-19 VACCINE ASTRAZENECA) in 1077 healthy adults 18 to 55 years of age in the UK. Trial participants are healthy and at increased risk for being exposed to the SARS-CoV-2 virus. Participants receive either a single IM dose or a 2- dose IM regimen of the low dose (LD) (~2.5 $x10^{10}$ vp) and/or the standard dose (SD) (~$5x10^{10}$ vp) of COVID-19 VACCINE ASTRAZENECA or the comparator, meningococcal vaccine (MenACWY). The participants will be followed for 12 months from the last vaccination.

COV002 (A phase II/III study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19): Phase II/III.

COV002 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (COVID-19 VACCINE ASTRAZENECA) in 10,812 participants in the UK. Trial participants are ≥ 18 years of age. In addition, a single arm group whereby up to 60 Human immunodeficiency virus (HIV) infected individuals who are stable on antiretroviral therapy will be recruited and receive COVID-19 VACCINE ASTRAZENECA vaccination. Participants are enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focuses on health care professionals and other adults with high potential for exposure to COVID-19. Participants receive a single IM dose or a 2-dose IM regimen of the LD (~$2.5x10^{10}$ vp) and/or the SD (~$5x10^{10}$ vp) of COVID-19 VACCINE ASTRAZENECA or the comparator, MenACWY, depending on the study group. The participants will be followed for 12 months from the last vaccination.

COV003 (A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine): Phase III.

COV003 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 Vaccine (COVID-19 VACCINE ASTRAZENECA) in 10416 participants in Brazil. Trial participants

are ≥ 18 years of age, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS CoV- 2 virus. Participants are randomised to receive either a 2-dose regimen of the SD (~5x10^{10} vp) of COVID-19 VACCINE ASTRAZENECA or, MenACWY or the MenACWY as the prime dose and saline placebo as boost dose by means of an IM injection. The participants will be followed for 12 months from the last vaccination.

COV004 (A Ib/II single-blinded, randomised, controlled study to determine safety, immunogenicity and efficacy of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in adults in Kenya): Phase Ib/II.

COV004 is an Oxford-sponsored, phase Ib/II trial single-blinded, randomised, controlled study of the SD (~5x10^{10} vp) of ChAdOx1 nCoV-19 (COVID-19 VACCINE ASTRAZENECA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial will be vaccine safety and immunogenicity of COVID-19 VACCINE ASTRAZENECA vaccine as compared to the rabies control vaccine, with vaccine efficacy (VE) against COVID-19 evaluated as a secondary endpoint. Approximately 400 healthy adults ≥ 18 years of age (approximately 40 participants in Phase Ib and 360 participants in Phase II) with high potential exposure to SARS-CoV-2 will be randomised. In the phase Ib part of the study the participants receive 1 IM dose of the SD (~5x10^{10} vp) COVID-19 VACCINE ASTRAZENECA or rabies vaccine as control. In the phase II part of the study a 2-dose regimen of the SD (~5x10^{10} vp) of COVID-19 VACCINE ASTRAZENECA or rabies vaccine will be distributed at day 84 (3 months). The participants will be followed for 12 months from the first vaccination.

COV005 (An adaptive phase I/II randomised placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARSCoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV): Phase I/II.

COV005 is an Oxford-sponsored, double-blind, multi-centre, randomised, placebo-controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 SARSCoV-2 vaccine (COVID-19 VACCINE ASTRAZENECA) in 2130 participants with and without HIV in South Africa. Trial participants aged 18-65 years will receive a 2-dose IM regimen of the SD (5-7.5 x10^{10} vp) of COVID-19 VACCINE ASTRAZENECA or saline placebo. The phase I study consists of two groups (HIV-uninfected adults; n=70, and HIV-infected adults; n=100), will be evaluated for safety and immunogenicity. The phase II part of the study will target 1900 participants (HIV-uninfected) and will be evaluated for immunogenicity and efficacy. The total duration of the study will be 12 months from the day of enrolment for all participants.

Efficacy, safety, and immunogenicity results from pooled analyses including data fromCOV001, COV002, COV003 and COV005 studies:

The evaluation of the efficacy, immunogenicity and safety of COVID-19 VACCINE ASTRAZENECA for prevention of COVID-19 is based on the pooled data from 4 ongoing clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (South Africa). The primary efficacy analysis demonstrated effective protection of COVID-19 VACCINE ASTRAZENECA against COVID-19 with a VE of 66.73% (95% confidence interval [CI]: 57.41%, 74.01%) ($p< 0.001$) from 15 days after the second dose in seronegative participants receiving two standard doses (SDSD) or 1 low dose and 1 standard dose (LDSD). The pooled analyses demonstrated that COVID-19 VACCINE ASTRAZENECA provides complete protection against COVID-19 hospital admission ≥ 22 days after the first SD dose in the seronegative analysis set. For the SDSD regimen, it was demonstrated that vaccine protection begins from 22 days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a flexible window between 4 to 12 weeks. COVID-19 VACCINE ASTRAZENECA elicited a strong induction of humoral immunogenicity, as measured by different serological assays following the first dose and the second dose of COVID-19 VACCINE ASTRAZENECA regardless the presence of co-morbid conditions at baseline, country, and age at screening. In summary, pooled analyses of the 4 ongoing University of Oxford-sponsored studies demonstrated that a low incidence of SAEs in both the AZD1222 and control groups, with no difference in either frequency or type between the treatment groups The vaccine was well tolerated in pooled safety analyses. There was not a significant change in the safety profile during the reporting period.

COV006 (A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents [aged 6-17]): Phase II.

COV006 is an Oxford-sponsored, Phase II, single-blinded, active-controlled, randomised study in approximately 300 healthy children and adolescents aged 6-17 years in the UK, of 2 doses 4 or 12 weeks apart of ChAdOx1 nCoV-19 (COVID-19 VACCINE ASTRAZENECA) or active control (licensed Meningococcal B vaccine) administered IM. The study will assess safety, tolerability and immunogenicity of a SD dose (~$5x10^{10}$ vp) of ChAdOx1 nCoV-19. The total duration of the study will be 12 months from the day of enrolment for all participants.

COV008 (A Phase I study to determine safety, tolerability and immunogenicity of intranasal administration of the COVID vaccine ChAdOx1 nCOV-19 in healthy UK adults): Phase I.

COV008 is an Oxford-sponsored, Phase I, open label, dose escalation study in up to 54 healthy adults in the UK. In group 1a adults aged 18-40 years were eligible, the other groups

included healthy adults aged 30-40 years. The study will investigate safety, tolerability and immunogenicity of one or two doses of intranasal ChAdOx1 nCOV-19 ($5x10^9$ vp, $2x10^{10}$ vp or $5x10^{10}$ vp), with randomisation between one and two dose groups. The total duration of the study will be 10 months from the day of enrolment for all participants.

COV009 (Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine): Long-term follow-up

COV009 is an Oxford-sponsored, follow-up study of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 coronavirus vaccine. Up to 1,077 participants will be eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment will be given during this Study. Study duration is 12 months.

D8110C00001 (A Phase III Randomised, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase III.

D8110C00001 is an AstraZeneca-sponsored, Phase III randomised, double-blind, placebo-controlled, multi-centre study assessing the safety, efficacy, and immunogenicity of COVID-19 VACCINE ASTRAZENECA compared to saline placebo for the prevention of COVID-19. Participants are adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19. A total of 32451 participants were randomised in a 2:1 ratio to receive 2 IM doses of either the SD (~$5x10^{10}$ vp) of COVID-19 VACCINE ASTRAZENECA or saline placebo 4 weeks apart. Randomization was stratified by age (18-65 years, and ≥ 65 years), with at least 25% of participants enrolled in the older age stratum. Safety will be assessed for the duration of the study. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730).

Efficacy and safety results from study D8110C00001

During the reporting period a further analysis of the primary endpoint was conducted using the Data cut-off date of 30 July 2021.

This analysis included 325 adjudicated events occurring ≥ 15 days post-second dose of study intervention in the fully vaccinated analysis set (FVS). There were 141 events in the COVID-19 VACCINE ASTRAZENECA group and 184 events in the placebo group, with a VE estimate of 66.98% and a lower bound of the 95% CI of 58.87%. This result was generally

consistent with the statistically significant result from the primary efficacy analysis using the data from the 05 March 2021 data cut-off. Of note, the incidence rate for the COVID-19 VACCINE ASTRAZENECA group was approximately 3-fold lower than for the placebo group (39.22 cases/1000 patient-years vs 118.75 cases/1000 patient-years, respectively).

Vaccine efficacy was also observed across age groups. In participants ≥ 18 to < 65 years of age, there were 135 events in the COVID-19 VACCINE ASTRAZENECA group and 165 events in the placebo group, with a VE estimate of 64.76% and a lower bound of the 95% CI of 55.73%. In participants ≥ 65 years of age in the FVS, there were 6 events in the COVID-19 VACCINE ASTRAZENECA group and 19 events in the placebo group, with a VE estimate of 86.35% and a lower bound of the 95% CI of 65.79%.

It should be noted that for the 6-month data analysis, median duration of follow-up after the second dose was longer for participants in the AZD1222 group compared with participants in the placebo group prior to vaccination with an authorized/approved vaccine (201.0 days and 78.0 days, respectively). The duration of follow-up for participants in the placebo group was impacted by unblinding and the receipt of an Emergency Use Authorization vaccine.

Safety results at the 6-month data cut-off were generally consistent with safety findings at the primary analysis, with no new or emerging safety issues identified. Overall, AZD1222 remains well-tolerated up to 6 months post dose. The AE profile continued to be consistent with AEs commonly observed following vaccine administration. The majority of AEs following administration of AZD1222 were mild or moderate in severity. In the AZD1222 group, a small proportion of SAEs and Adverse Event of Special Interest (AESIs) were reported, with no clinically meaningful findings.

In terms of humoral immunogenicity, the 6-month data are still under analysis.

D8111C00002 (A Phase I/II Randomised, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase I/II.

This is an AstraZeneca-sponsored, multicentre, randomised, double-blind, parallel-group, placebo-controlled, 52-week Phase I/II study. In this study, 256 eligible participants from Japan were randomised in a 3:1 ratio to receive 2 IM doses of either COVID-19 VACCINE ASTRAZENECA with $5x10^{10}$ vp (nominal) or placebo administered 4 weeks apart. The study has 2 cohorts with different age populations. Cohort C will include healthy participants aged 18 to 55 years. Cohort D will include healthy elderly participants aged ≥ 56 years. In Cohort D, the elderly population is further divided into 2 different age subgroups: aged 56 to 69 years (Subcohort D1) and aged ≥ 70 years (Subcohort D2). Regarding Cohorts C and D, 128 participants will be randomised in a 3:1 ratio to receive either COVID-19 VACCINE

ASTRAZENECA or placebo within each cohort. The participants will be followed for a period of 52-weeks from the first vaccination.

Immunogenicity and safety from study D8111C00002

In Japanese participants from Study D8111C00002, COVID-19 VACCINE ASTRAZENECA elicited strong humoral immune responses against SARS-CoV-2 (anti-Spike and anti-receptor-binding domain (RBD) there were no safety concerns during the clinical trial.

D7220C00001 (A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2): Phase II/III.

This is an AstraZeneca-sponsored, multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants. The participant population includes adults ≥18 years of age. A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 225 participants) to support exploratory analysis is these participants.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of IM administration of either COVID-19 VACCINE ASTRAZENECA (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Participants receiving a 2-dose primary vaccination will be dosed at intervals of 4 weeks (for COVID-19 VACCINE ASTRAZENECA and AZD2816) or 12 weeks (AZD2816 only). All study participants will be followed for safety for 180 days after administration of their last vaccination dose.

Interim analysis of safety and immunogenicity results from the previously vaccinated participants that have received a booster dose of AZD1222 or AZD2816 have been reported.

The safety (through Day 29) and reactogenicity (through Day 8) of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or an messenger ribonucleic acid (mRNA) vaccine, including for those in the Seronegative Safety Analysis Set, was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and

AZD2816. Analyses of data through to data cut-off, up to a maximum of 107 days after booster dose, did not identify any emergent safety issues.

Humoral immunogenicity data from the interim analysis indicate that a booster dose of either AZD1222 or AZD2816 in seronegative participants previously vaccinated with AZD1222 or an mRNA vaccine generates a strong humoral response to SARS-CoV-2 by 28 days after the booster is administered.

7.2.2 Overall Safety, Efficacy and immunogenicity

The safety, efficacy and immunogenicity of a two-dose regimen of COVID-19 VACCINE ASTRAZENECA has been currently investigated in 11 ongoing clinical trials. The initial VE against symptomatic disease of 66.7% (95% CI: 57.4%, 74.0%) ($p < 0.001$) demonstrated in a pooled analyses of four trials (COV001, COV002, COV003, COV005) was confirmed in a large study conducted mainly in the United States of America (USA) (VE=74%; 95CI: 65.34, 80.47). The vaccine has also shown to be highly immunogenic after a single dose, with increase in seroconversion after a second dose. Moreover, adults (including those over the age of 65 years) with pre-existing comorbidity showed similar VE and immune responses when compared to the general population. The safety of COVID-19 VACCINE ASTRAZENECA has been evaluated in ongoing clinical trials. No safety concerns have arisen from these ongoing COVID-19 VACCINE ASTRAZENECA/AZD2816 clinical trials.

7.3 Long-term follow-up

All patients included in COV001, COV002, COV003, COV005, USA (D8110C00001) and Japan (D8111C00002) studies have completed the defined treatment regimen and are being actively followed for at least 12 months as part of the protocol. Details can be found in Section 7.2.

Study participants enrolled in the ongoing COVID-19 VACCINE ASTRAZENECA clinical development programme, have not all completed one year follow up following last vaccination and 12-months follow up data are not yet available. The longest follow up safety data available from clinical trials was obtained from Study D8110C00001. Safety results at the 6-month data cut-off were generally consistent with safety findings at the primary analysis, with no new or emerging safety issues identified.

7.4 Other therapeutic use of medicinal product

During the reporting period there were no clinically important safety findings identified from other programmes that follow a specific protocol with solicited reporting.

7.5 New safety data related to fixed-combination therapies

This section is not applicable as COVID-19 VACCINE ASTRAZENECA is not approved or under development as part of a fixed-combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

No relevant safety information or information with potential impact on the benefit or risk evaluations arose from AstraZeneca sponsored non-interventional studies of COVID-19 VACCINE ASTRAZENECA during the reporting period.

A listing of AstraZeneca sponsored non-interventional Post-Authorisation Safety Studies (PASS) completed or ongoing during the reporting period is provided in Appendix 4.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other clinical trials

During the reporting period, a couple of noteworthy publications have been cited and are briefly described below.

The first study (Flaxman et al 2021) assessed the persistence of immunogenicity after a single dose of ChAdOx1 nCoV-19 (AZD1222) after an extended interval (44–45 weeks) between the first and second dose, and response to a third dose as a booster given 28–38 weeks after the second dose. The two dose cohort consisted of 321 participants and 90 participants were enrolled for the third booster part of the study. The findings of this study and the conclusions reached by the authors indicate that an extended interval between doses leads to an increase in antibody titres and that the administration of a third booster dose following the primary series led to an increase in antibody titres above those observed after a second dose, a level that correlates with high efficacy and also boosts T-cell responses. In terms of reactogenicity, this was lower both after the second and third (booster) doses relative to the first dose, consistent with the known safety profile of AZD1222.

Secondly, the COV-BOOST trial (Munro et al 2021) is investigating the use of seven different COVID-19 vaccines when given as a third ‘booster’ dose, including three of them as half doses, on participants representative of the UK population who have received 2 doses of AZD1222 or BNT162b2. Results of this study indicated that boosted immunity was identified after ChAd/ChAd as measured by anti-spike Immunoglobin (IgG) and neutralising assays. Six vaccines (including AZD1222) showed boosted immunity after BNT/BNT irrespective of age. Furthermore, the authors of the study indicated that reactogenicity results were similar between those aged 30–69 years and those aged 70 years and older. Fatigue and pain were the

most common solicited local and systemic adverse events, experienced more in people aged 30–69 years than those aged 70 years or older.

No information relevant to the benefit-risk assessment of COVID-19 VACCINE ASTRAZENECA was identified from any other clinical trial or study sources, during the reporting period.

9.2 Vaccination errors

Case reports of vaccination error where no other AEs have been reported do not fulfil the criteria for inclusion in the tabulation in Appendix 2 but are included in the searches below.

The search strategy for vaccination errors includes the following PT's:

- PTs in the SMQ Medication errors and
- PT's: Device failure; Device deployment issue; Prescription drug used without a prescription; Device delivery system issue; Product advertising issue; Counterfeit product administered; Device mechanical issue; Device safety feature issue; Device environmental compatibility issue; Device data issue; Device temperature issue; Device user interface issue; Device signal transmission issue; Device wireless communication issue; Unevaluable device issue.

Interval Period (29 June 2021 – 28 December 2021)

A total of 7805 case reports (7451 initial and 354 follow up), including 8434 vaccination error AEs, have been identified during the reporting period, which represents 72% cases of the cumulative (10794). Of those, 7805 case reports 838 were reported as serious (229 case reports were medically confirmed and 609 were consumer reports). In 5461 (70.96%) of the 7805 cases reports no other AEs were reported in connection with the vaccination error. AEs were reported in the remaining 2344 (30%) case reports.

Out of the 2344 cases with other AEs, 799 (34.08%) cases were serious and 1545 (65.91%) were non-serious. Of the 2344 cases, 515 (34.08%) were medically confirmed and 1829 (78.02%) were non-medically confirmed. Out of 799 cases, the seriousness criteria were fatal/death in 31 case reports, hospitalisations in 301 cases and the remaining were medically important.

Out of 2344 case reports there were 13404 events (3045 serious and 10400 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 17).

Table 17 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 December 2021

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	3260	502	2766	24.32
Injury, poisoning and procedural complications	2741	269	2476	20.45
Nervous system disorders	1827	631	1207	13.63
Musculoskeletal and connective tissue disorders	1195	274	929	8.92
Gastrointestinal disorders	650	151	500	4.85
Surgical and medical procedures	462	43	419	3.45
Respiratory, thoracic and mediastinal disorders	452	166	287	3.37
Skin and subcutaneous tissue disorders	411	102	311	3.07
Investigations	379	100	280	2.83
Infections and infestations	319	91	229	2.38
Psychiatric disorders	313	72	241	2.34
Vascular disorders	260	147	114	1.94
Eye disorders	212	74	138	1.58
Cardiac disorders	176	102	75	1.31
Reproductive system and breast disorders	148	48	101	1.10
Ear and labyrinth disorders	128	43	86	0.95
Blood and lymphatic system disorders	97	60	37	0.72
Metabolism and nutrition disorders	84	25	59	0.63
Immune system disorders	78	33	45	0.58
Social circumstances	70	26	44	0.52
Renal and urinary disorders	51	32	19	0.38
Pregnancy, puerperium and perinatal conditions	29	27	2	0.22
Product issues	19	1	18	0.14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18	13	5	0.13
Hepatobiliary disorders	17	9	8	0.13

Table 17 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 December 2021

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Congenital, familial and genetic disorders	4	4		0.03
Endocrine disorders	4		4	0.03
Total	**13404**	**3045**	**10400**	**100**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 17. The AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015).

Most commonly reported AEs (≥50) in the 2344 vaccination error cases were Headache (838), Pyrexia (798), Pain (437), Fatigue (428), Pain in extremity (397), Chills (335), Myalgia (297), Arthralgia (269), Malaise (244), Asthenia (241), Dizziness (217), Nausea (193), Injection site pain (151), Dyspnoea (146), Paraesthesia (136), Diarrhoea (136), Vomiting (120), COVID-19 (111), Hypoaesthesia (99), Feeling abnormal (92), Cough (88), Chest pain (88), Rash (85), Application site pain (83), Peripheral swelling (81), Thrombosis (76), Erythema (74), Muscular weakness (72), Back pain (72), Vaccination site pain (71), Pruritus (68), Influenza like illness (68), Tremor (66), Gait disturbance (64), Limb discomfort (62), Insomnia (60), Vision blurred (59), Tinnitus (58), Hyperhidrosis (55), Contusion (55), Abdominal pain (55), Somnolence (54), Illness (54), Nasopharyngitis (52), Hypersensitivity (52), Oropharyngeal pain (51).

During the reporting period there was one case each reported with Gastroenteral (GE), Infiltration (IF), “Intracardiac” (IC), Intracavernous (ICS), Intradiscal (intraspinal) (IS), Nasal (IN), Respiratory (inhalation) (IH), Transmammary (TM) routes of administration that were associated with AE’s and 1 case was reported with Intraocular (IOC) without AE. There were 2 cases each reported with Auricular (otic) (EAR), Intravenous bolus (PU), Subdermal (SD), Transplacental (TPL) routes that were associated with AE and 2 cases were reported with Intrameningeal (IMEN) route (1 with AE and 1 without AE). Five cases were reported with cutaneous (CU) route, 6 cases were reported with Parenteral (PAR) route, 8 cases with oral (PO) route and 12 cases with Intradermal route that were associated with AE. There were 72 cases reported with Intravenous (IV) (70 with AE and 2 without AE), 108 cases were reported with subcutaneous route (SQ) (105 with AE and 3 without AE) and 7450 cases were reported with intramuscular (2113 with AE and 5427 without AE). Additionally, there were 35 cases where the route of administration was unspecified of these, 8 were associated with AE and 27 without AE.

Cumulative Review (29 December 2020 – 28 December 2021)

A total of 10794 case reports, including 11865 vaccination error AEs, have been identified during the cumulative period. Of those, 10794 case reports 1172 were considered serious (289 case reports were medically confirmed and 883 were consumer reports). In 7476 (69.2%) of the 10794 cases reports no other AEs were reported in connection with the vaccination error. Adverse events were reported in the remaining 3318 (30.7%) case reports.

Out of the 3318 cases with adverse events, 1121 (33.78%) cases were serious and 2197 (66.21%) were non-serious. Of the 3318 cases, 717 (21.60%) were medically confirmed and 2601 (78.39%) were non-medically confirmed. Out of 1121 cases, the seriousness criteria were fatal/death in 36 case reports, hospitalisations in 366 cases and the remaining were medically important.

A review of all the cases with seriousness fatal/death received during the cumulative and in the reporting period suggested fatal outcome in 12 cases in association with vaccination error.

Out of 3318 case reports there were 18293 events (4393 serious and 13943 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 18).

Table 18 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 December 2021

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	4768	869	3909	26.06
Injury, poisoning and procedural complications	3800	451	3353	20.77
Nervous system disorders	2520	873	1658	13.78
Musculoskeletal and connective tissue disorders	1641	388	1261	8.97
Gastrointestinal disorders	896	242	655	4.90
Respiratory, thoracic and mediastinal disorders	560	205	356	3.06
Skin and subcutaneous tissue disorders	548	164	386	3.00
Surgical and medical procedures	522	51	471	2.85
Investigations	492	128	365	2.69
Infections and infestations	421	128	294	2.30

Table 18 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 December 2021

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Psychiatric disorders	396	93	303	2.16
Vascular disorders	316	181	136	1.73
Eye disorders	272	99	173	1.49
Cardiac disorders	212	120	93	1.16
Reproductive system and breast disorders	174	59	116	0.95
Ear and labyrinth disorders	158	55	104	0.86
Metabolism and nutrition disorders	120	37	83	0.66
Blood and lymphatic system disorders	117	70	47	0.64
Immune system disorders	94	43	51	0.51
Social circumstances	81	32	49	0.44
Renal and urinary disorders	61	35	26	0.33
Pregnancy, puerperium and perinatal conditions	39	37	2	0.21
Product issues	38	3	35	0.21
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20	15	5	0.11
Hepatobiliary disorders	18	10	8	0.10
Congenital, familial and genetic disorders	5	5		0.03
Endocrine disorders	4		4	0.02
Total	**18293**	**4393**	**13943**	**100**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 19. The AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015).

Most frequently reported AEs ≥ 50 within the 3318 case reports of vaccination error were Headache (997), Pyrexia (996), Chills (514), Fatigue (496), Pain (485), Pain in extremity (401), Myalgia (361), Arthralgia (291), Malaise (282), Dizziness (266), Asthenia (258), Nausea (249), Injection site pain (211), Vomiting (147), Diarrhoea (146), Dyspnoea (136), Paraesthesia (129), COVID-19 (113), Hypoaesthesia (101), Feeling abnormal (89), Tremor (85), Influenza like illness (85), Cough (84), Vaccination site pain (80), Chest pain (79), Rash

(78), Hyperhidrosis (77), Decreased appetite (75), Pruritus (74), Back pain (72), Abdominal pain (72), Thrombosis (71), Peripheral swelling (69), Limb discomfort (66), Insomnia (66), Application site pain (66), Somnolence (64), Feeling cold (60), Muscular weakness (59), Contusion (58), Erythema (57), Vision blurred (55), Oropharyngeal pain (54), Illness (54), Tinnitus (53), Heart rate increased (53), Gait disturbance (53), Nasopharyngitis (51), Palpitations (50), Injection site erythema (50).

During the cumulative period, there was one case each reported with Gastroenteral (GE), Infiltration (IF), Intra-articular (IJ), Intracardiac (IC), Intracavernous (ICS), Intradiscal (intraspinal) (IS), Intrasynovial (ISYN), Respiratory (inhalation) (IH), Subconjunctival (SCON) and Other (OTHER) routes that were associated with AE. 2 cases each were reported with Auricular (otic) (EAR), Intravenous bolus (PU), Nasal (IN), Subdermal (SD), Transplacental (TPL) routes of administration which were associated with AE's and 2 cases were reported with Intrameningeal (IMEN) route (1 with AE and 1 without AE). There were 3 cases reported with Transmammary (TM) route, 4 cases with Intraocular (IOC) (3 with AE and 1 without AE), 8 cases with Parenteral route (PAR), 10 cases with Cutaneous (CU) route, 13 cases with oral (PO) route and 20 cases with Intradermal route of administration that were associated with AE. A total of 102 cases were reported with Intravenous (IV) route (99 with AE and 3 without AE) and 177 cases with subcutaneous (SQ) route (168 with AE and 9 without AE). There were 10385 cases reported with intramuscular route of administration (2964 with AE and 7421 without AE). Additionally, there were 50 cases where the route of administration was unspecified of these, 11 were associated with AE and 39 without AE.

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Accidental	Accidental exposure to product	7	12	16	14	4	92	4	98	132
	Accidental exposure to product packaging	0	1	0	1	0	0	0	0	1
	Accidental underdose	0	0	1	4	0	4	0	15	20
	Exposure to contaminated device	0	0	1	0	0	0	0	0	1
	Intercepted accidental exposure to product by child	0	0	0	0	0	0	0	1	1
Administration errors	Counterfeit product administered	0	0	0	0	0	1	0	1	1
	Drug administered in wrong device	0	0	0	0	1	1	1	1	2
	Drug monitoring procedure not performed	0	0	0	0	0	0	0	1	1
	Drug titration error	0	1	0	1	0	0	0	0	1
	Duplicate therapy error	0	0	0	0	0	2	0	3	3
	Inadequate aseptic technique in use of product	0	0	1	1	0	0	0	0	2
	Incorrect product formulation administered	0	1	0	1	2	21	2	22	25
	Incorrect product administration duration	0	5	0	6	0	5	0	13	19

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Incorrect route of product administration	32	305	49	524	0	40	0	57	630
	Lack of vaccination site rotation	0	0	1	0	0	0	0	0	1
	Product administration interrupted	0	2	0	2	0	0	0	0	2
	Product administered at inappropriate site	28	33	39	59	2	11	2	18	118
	Product administered to patient of inappropriate age	5	75	7	106	5	537	6	578	697
	Product administration error	8	31	13	51	1	66	2	122	188
	Product monitoring error	0	3	1	3	0	0	0	2	6
	Wrong route	0	1	0	2	0	0	0	0	2
	Wrong technique in device usage process	0	0	0	2	0	0	0	0	2
	Wrong technique in product usage process	1	14	5	20	0	4	1	11	37
Contraindication	Contraindication to vaccination	2	7	5	7	5	100	3	73	88
	Contraindicated product administered	0	2	3	3	0	1	0	1	7
	Contraindicated product prescribed	1	2	8	3	0	0	0	0	11

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Contraindication to medical treatment	0	0	0	1	0	0	0	0	1
	Documented hypersensitivity to administered product	0	0	0	0	0	0	0	2	2
	Labelled drug-drug interaction issue	2	1	2	1	0	0	0	0	3
	Labelled drug-drug interaction medication error	1	0	1	0	0	0	0	0	1
Equipment	Device use issue	0	0	1	0	0	0	0	0	1
	Device connection issue	0	0	0	0	0	2	0	3	3
	Device maintenance issue	0	0	0	0	0	0	0	1	1
	Device use confusion	0	0	0	1	0	0	0	0	1
	Device use error	0	0	0	0	0	0	0	1	1
	Injury associated with device	0	2	8	8	1	0	1	0	17
	Medical device monitoring error	0	0	0	0	0	0	0	1	1
	Needle issue	0	3	1	8	0	1	1	7	17
	Syringe issue	0	1	0	4	0	2	0	9	13
	Wrong device used	0	0	0	2	0	0	0	0	2
General error	Medication error	25	256	44	429	1	329	3	848	1324

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Occupational exposure to product	1	0	2	4	0	3	0	8	14
	Product use issue	7	27	9	36	0	10	0	15	60
	Vaccination error	9	43	11	50	0	134	0	162	223
Inappropriate schedule	Inappropriate schedule of product administration	11	611	13	712	1	791	2	978	1705
	Wrong schedule	0	5	0	7	0	6	0	19	26
Incorrect dose	Accidental overdose	2	1	4	4	0	4	1	16	25
	Booster dose missed	0	8	0	8	0	21	0	24	32
	Dose calculation error	2	4	2	8	0	2	0	2	12
	Extra dose administered	3	12	3	14	0	27	0	63	80
	Incorrect dose administered by device	0	0	0	0	0	2	0	2	2
	Incorrect dose administered by product	0	1	0	1	0	0	0	0	1
	Incorrect product dosage form administered	1	1	1	1	0	0	0	0	2
	Incorrect dose administered	12	106	17	152	5	483	5	607	781
	Incomplete course of vaccination	7	150	8	158	1	158	1	174	341
	Incorrect dosage administered	0	2	0	3	0	10	0	28	31

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Overdose	32	45	54	60	0	15	0	36	150
	Prescribed overdose	0	0	0	1	0	0	0	0	1
	Prescribed underdose	0	2	0	2	0	1	0	2	4
	Product dose omission issue	5	217	6	240	0	187	0	211	457
	Product dose omission in error	0	12	1	16	0	5	0	11	28
	Underdose	0	11	1	20	2	105	4	213	238
Off-Label	Product use in unapproved indication	2	3	2	4	0	0	0	0	6
Potential errors	Circumstance or information capable of leading to device use error	0	0	0	0	0	1	0	2	2
	Circumstance or information capable of leading to medication error	1	65	4	83	1	119	1	166	254
	Intercepted product storage error	0	1	0	2	0	43	0	228	230
	Intercepted medication error	1	8	1	11	0	71	0	304	316
	Intercepted product preparation error	0	0	0	0	0	4	0	6	6
	Intercepted product administration error	0	0	1	3	0	3	0	11	15
Preparation error	Product preparation error	0	0	0	0	0	21	0	22	22

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product reconstitution quality issue	0	0	0	0	0	2	0	2	2
	Prescription drug used without a prescription	0	0	3	0	0	0	0	0	3
	Product preparation issue	0	6	0	6	0	12	0	14	20
Prescribing error	Transcription medication error	0	2	0	4	0	2	0	2	6
Product labelling/packaging	Product label confusion	0	0	0	1	0	1	0	3	4
	Product label issue	0	0	0	2	0	3	0	1	3
	Product name confusion	0	0	1	1	0	2	0	2	4
	Product packaging confusion	0	3	0	3	0	0	0	0	3
	Product packaging issue	0	0	0	0	0	1	0	1	1
	Product barcode issue	0	0	1	0	0	0	0	0	1
	Product confusion	0	1	0	1	0	2	0	2	3
	Product identification number issue	0	0	0	0	0	0	0	2	2
	Product lot number issue	0	0	0	0	0	1	0	6	6
Product quality	Poor quality product administered	3	2	3	2	0	12	1	25	31
	Product use complaint	0	0	0	0	0	2	0	2	2
Storage/dispensing	Device dispensing error	0	0	0	0	0	2	0	2	2

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Expired product administered	5	95	23	107	1	750	1	763	896
	Product communication issue	0	1	0	3	0	4	0	7	10
	Product dispensing error	2	3	12	8	0	1	0	4	24
	Product dispensing issue	0	0	0	0	0	0	0	1	1
	Product prescribing error	0	0	1	6	0	8	0	16	23
	Product prescribing issue	0	0	0	1	0	1	0	2	3
	Product selection error	0	0	0	0	1	0	1	2	3
	Product substitution error	0	0	0	0	0	0	0	1	1
	Product storage error	0	12	0	39	0	106	0	440	479
	Product temperature excursion issue	0	0	0	3	0	124	0	397	400
Wrong vaccine	Wrong product administered	3	60	5	68	11	1316	11	1330	1414
	Interchange of vaccine products	24	435	27	460	2	983	2	1011	1500
	Unintentional use for unapproved indication	0	0	0	0	0	0	0	1	1
	Wrong dosage form	0	1	0	1	0	0	0	0	1
	Wrong dose	0	2	0	2	0	1	0	1	3
	Wrong drug	0	0	0	0	0	1	0	5	5

Table 19 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Wrong patient received product	0	0	0	1	0	0	0	0	1
Other	Exposure via partner	0	0	1	0	0	0	0	0	1
	Exposure via unknown route	0	0	0	1	0	0	0	0	1
Grand Total		**245**	**2716**	**424**	**3584**	**47**	**6782**	**56**	**9244**	**13310**

Seriousness was evaluated at the event level, which may differ from the seriousness assigned to the report level.

Cases with no reported AEs are also included.

In the above table 86 events were not included as these were considered invalid during interval period.

Case reports may include more than one vaccination error AE.

AE Adverse Event; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Summary and Conclusion

Most frequently reported vaccination errors along with other AEs included Inappropriate schedule of product administration, Incorrect route of product administration, Interchange of vaccine products, Medication error, Product dose omission issue, Incorrect dose administered, Incomplete course of vaccination, and Expired product administered. Most of the AEs reported for these vaccination errors were related to the reactogenicity events such as Pyrexia, Headache, Chills, Fatigue, Pain, Pain in extremity, Myalgia, Arthralgia, and Malaise. There was no clustering of AEs or AESI's with any of the vaccination error types.

A review of all the vaccination error AE reports received during interval and cumulative period did not demonstrate any medication error-emergent safety pattern associated with COVID-19 VACCINE ASTRAZENECA. No new relevant patterns of vaccination errors or new safety concerns were identified during the reporting period.

Reports related to COVID-19 VACCINE ASTRAZENECA vaccination errors will continue to be monitored by AstraZeneca through standard surveillance activities.

10 NON-CLINICAL DATA

There were no major safety findings from any AstraZeneca-sponsored non-clinical in vivo and in vitro studies of COVID-19 VACCINE ASTRAZENECA ongoing or completed during the reporting period.

11 LITERATURE

AstraZeneca conducts comprehensive reviews of peer-reviewed published scientific literature and unpublished manuscripts routinely on an ongoing basis. The search strategy includes COVID-19 VACCINE ASTRAZENECA and other COVID-19 vaccines in order to identify potential class related findings.

Relevant literature articles containing new and significant safety findings relevant to COVID-19 VACCINE ASTRAZENECA published during the review period were retrieved. Articles of interest related to event reviews completed as part of Health Authority requests, Important identified and Potential risks or Missing information have been included within the review of those safety concerns throughout section 15.2 and section 16. Other articles containing new and significant safety findings for other topics of interest (general AE rates, special populations, etc) are summarized in Appendix 10.

12 OTHER PERIODIC REPORTS

There have been no significant findings from other periodic reports provided by other parties during the reporting period.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

On 26 November 2021, the WHO designated the Omicron variant (B.1.1.529) a variant of concern (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Researchers at the University of Oxford have issued a preprint regarding the neutralisation of Omicron by large panel of sera, including from convalescent patients and from vaccinees receiving 2 or 3 doses of COVID-19 VACCINE ASTRAZENECA or the Pfizer/BioNtech BNT16b2 vaccine (Dejnirattisai et al 2021).

AstraZeneca has also collaborated with the University of Oxford researchers who conducted these assessments and with the UK Health Securities Agency (UKHSA), formerly called Public Health England) to analyse sera from participants in ongoing AstraZeneca-sponsored study D7220C00001 who had received 3 doses of COVID-19 VACCINE ASTRAZENECA.

Collectively, these preliminary live virus neutralisation data suggest that 2-dose primary series immunisation with COVID-19 VACCINE ASTRAZENECA will likely provide limited protection against infection with the Omicron variant. These data also suggest that adding a third booster dose of COVID-19 VACCINE ASTRAZENECA will likely provide increased protection against infection with the Omicron variant, though still less protection than as against the original Wuhan-Hu-1 strain or other variants of concern.

Despite the higher risk of breakthrough infection with Omicron due to lower nAb titres, it is considered likely that clinically meaningful protection against hospitalisation and severe infection would be maintained. Detectable levels of nAb to the Omicron variant after boost, as well as robust humoral, cellular, and mucosal recall responses to vaccination, should offer protection from severe disease. Moreover, it is anticipated that COVID-19 VACCINE ASTRAZENECA -induced T cell responses likely will be less affected than antibody responses, given T cell receptors (TCR) sequencing analysis has identified the immunodominant region of Spike recognised by CD8 T cells (Swanson et al 2021), which contains no mutations in the Omicron variant.

14 LATE BREAKING INFORMATION

Post the data-lock for this PBRER, AstraZeneca updated the CDS with the following additional safety-related changes:

- On 06 January 2022, Section 4.6 (Pregnancy and lactation) was updated to reflect current safety data regarding vaccine administration in pregnancy women, based on AstraZeneca global surveillance database, the pregnancy registry and literature. The recommendation was updated to consider the use of COVID-19 VACCINE ASTRAZENECA during pregnancy when the benefits outweigh the risks.

- On 17 January 2022, Section 4.6 (Pregnancy and lactation) was further updated to reflect current non-clinical, clinical and post-marketing data on the use of COVID-19 VACCINE ASTRAZENECA during breastfeeding.
- On 04 February 2022, Section 4.2 (Posology and method of administration), Section 4.4 (Special warnings and special precautions for use) and Section 4.8 (Undesirable effects) were updated to support changes to the recommendation for use of COVID-19 VACCINE ASTRAZENECA as a booster dose (third dose) after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).

In addition, 2 signals were validated after the data-lock of this PBRER:

- **Hypoaesthesia/Paraesthesia:** AstraZeneca received a signal from Therapeutic Goods Administration (TGA), Australia, to add hypoaesthesia and paraesthesia as ADRs to the local label for COVID-19 VACCINE ASTRAZENECA as these were the most commonly reported adverse reactions reported to TGA for all COVID-19 vaccines, including COVID-19 VACCINE ASTRAZENECA. AstraZeneca further reviewed this topic, and this signal was internally validated on 25 January 2022. On 31 January 2022, AstraZeneca considered that the overall data support a causal relationship between COVID-19 VACCINE ASTRAZENECA and hypoaesthesia/paraesthesia. CDS Section 4.8 is currently under revision to include hypoaesthesia/paraesthesia as ADRs. This revision is in the late stage of being finalized.

- **Guillain-Barré Syndrome (GBS):** The signal for GBS was re-opened based on new information from retrospective analysis (Patone et al 2021 and Keh et al 2022) as well as well-documented case reports of GBS with COVID-19 VACCINE ASTRAZENECA from the published literature. AstraZeneca internally validated the signal for GBS on 10 February 2022 and is currently undergoing evaluation as per AstraZeneca's signal detection and evaluation processes. Conclusions and any recommended actions for this signal will be communicated in the next PSUR, or earlier as necessary.

15 OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)

15.1 Overview of Validated Signals (New, Ongoing or Closed)

AstraZeneca is required to carry out pharmacovigilance on a routine basis according to the legislation. Routine pharmacovigilance is described in the pharmacovigilance system master file. However, a summary of signal identification is provided below.

Signals may be identified during:

- Review of individual case safety reports (ICSRs) arising from marketed use of the medicinal product or during clinical trials
- Regular analysis of aggregate ICSR data, including statistics of disproportionate reporting applied to the AstraZeneca global safety database and, as appropriate, publicly available databases of AEs (the US Food and Drug Administration Adverse Event Reporting System, the World Health Organisation VigiBase and the Eudravigilance Data Analysis System databases)
- Regular review of published biomedical articles and conference abstracts
- Review of results arising from AstraZeneca-sponsored trials and externally-sponsored scientific research (previously referred to as investigator-sponsored trials)
- Review of reports from the product complaints management system (ie, product quality complaints)

Safety-related enquiries from Health Authorities, healthcare professionals, and consumers are also considered a source of signals. Relevant findings from preclinical trials and new safety information on products with the same or similar modes of action to the medicinal product are also considered. Per AstraZeneca signal management process, any health authority request or signal notification is evaluated internally and considered a signal. If the evaluation of the safety topic determines a signal does not exist, then AstraZeneca will keep the term under close surveillance, requiring more frequent evaluation as part of routine surveillance activities for the product. If as a result of increased surveillance and evaluation of additional sources of data that evidence shows a potential causal association the events will be categorised as a validated signal and further assessment before determining an appropriate action.

The above are considered the most likely sources of signals, however relevant information from other sources is not excluded from consideration.

In the analysis of aggregate ICSRs arising from marketed use of AstraZeneca products, qualitative and pre-defined quantitative criteria are applied to the data in order to identify signals for evaluation. Quantitative analysis includes the use of algorithms to generate statistics of disproportionate reporting, including significant changes in these statistics over time. The initial evaluation of identified signals may lead to a more detailed evaluation and if a potential new risk is identified, a detailed review is undertaken by a scientific and medical forum.

A tabulation of **validated** signals that were ongoing or closed during the reporting period is presented in Appendix 3. In the previous PSUR, the validated signal of Thrombotic events with thrombocytopenia was included in Table 14 of Section 15.1, but was not included in Table 1 of Appendix 3. Upon investigation, the MAH discovered that the table of validated signals provided in Appendix 3 in the previous PSUR was generated using an incorrect

reporting interval. A corrected table of validated signals for the previous PSUR review period (29 December 2020 – 28 June 2021) has been provided in Appendix 3.

There were 2 validated signals that were either ongoing or closed during the reporting period. The validated signals are provided in Table 20 along with a cross-reference, where applicable, to the sections of the PBRER where further detail is provided and reference to the regulatory procedure document where the signal as previously assessed (if applicable).

Table 20 Summary of the validated signals that were ongoing or closed during the reporting period[a]

Validated Signal	Ongoing or Closed at the DLP of the PBRER	Section of the PBRER where additional detail is provided	Reference Regulatory Procedure Number(s)
Cerebral Venous Sinus Thrombosis (CVST) without thrombocytopenia	Closed	16.2.2	EMEA/H/C/005675/IB/0056
Guillain-Barré Syndrome (GBS)[b]	Closed	14 16.2.4	EMEA/H/C/005675/IB/0034 and EMEA/H/C/005675/IB/0044

DLP Data Lock Point, PBRER Periodic Benefit-Risk Evaluation Report.

[a] A signal for hypoaesthesia/paraesthesia was validated and closed during the Late-breaking period of this PSUR. Refer to Section 14 for additional information.

[b] The signal for GBS was re-opened during the Late breaking period of this report. See Section 14 for additional information.

15.2 Health Authority requests

Based on requests from Regulatory Authorities, AstraZeneca is requested to provide an update in the PBRER and a review of reports of the following topics

- Acute disseminated encephalomyelitis (ADEM, Section 16.3.1.1.1)
- Acute macular neuroretinopathy (AMN, Section 15.2.1)
- Adult-onset Still's disease (Section 15.2.2)
- Autoimmune hepatitis (Section 15.2.3)
- Blood pressure increased (Section 15.2.4)
- Booster dosing (Section 15.2.5)
- Capillary leak syndrome (CLS, Section 15.2.6)
- Cerebrovascular events (Section 15.2.7)
- Deep vein thrombosis (DVT) without thrombocytopenia, Section 15.2.8)
- Encephalitis, including fatal (Section 16.3.1.1.2)

- Hearing loss (Section 15.2.9)
- Hemophagocytic lymphohistocytosis (Section 15.2.10)
- Menstrual disorders (Section 15.2.11)
- Multisystem inflammatory syndrome in children and adults (MIS – C/A, Section 15.2.12)
- Myocarditis and Pericarditis (Section 15.2.13)
- Neuralgic amyotrophy (Section 15.2.14)
- Pulmonary embolism (PE) without thrombocytopenia (Section 15.2.15)
- Photophobia (Section 15.2.16)
- Retinal arterial/venous thrombosis, embolism or occlusion (Section 15.2.17)
- Sarcoidosis (Section 15.2.18)
- Subacute thyroiditis (Section 15.2.19)
- Tinnitus (Section 15.2.20)
- Transverse myelitis (Section 16.3.1.1.3)
- Vertigo (Section 15.2.21)
- Viral herpes infection (Section 15.2.22)
- Vulval ulceration (Section 15.2.23)

The review and summary of these topics is provided in the corresponding sections of this PBRER, as indicated.

15.2.1 Acute macular neuroretinopathy (AMN)

Request

AstraZeneca received the following requests from PRAC in the Assessment Report (AR) for the 7th and 8th SSRs (review periods: 01 August 2021 – 30 September 2021 and 01 October 2021 – 30 November 2021 respectively):

"Acute macular outer retinopathy (AMOR) / Acute macular neuro-retinopathy (AMN) / Paracentral acute middle maculopathy (PAMM): a review of cases, an update of literature findings."

"Acute macular neuro-retinopathy (AMN) / Paracentral acute middle maculopathy (PAMM): The MAH should continue to closely monitor cases of AMN/PAMM and present updates in the next PSURs. The cases should be reviewed by an expert panel of ophthalmologists, who should comment both on causality and diagnosis for each case. The MAH is asked to apply the WHO-UMC criteria correctly and to also include the verbatim term 'Paracentral acute middle maculopathy' in the search criteria. Additionally, an Observed versus Expected (O/E) analysis for AMN/PAMM with various risk windows and taking into account the best available background incidence rate(s), should be provided."

AstraZeneca's response to these requests is provided below.

Review of Cases

A cumulative search of the cases of 'Acute Macular Neuroretinopathy' (AMN) including verbatim term 'Paracentral Acute Middle Maculopathy' with MedDRA v24.1. The cut-off date was 28 December 2021. The review of the cases was performed applying the WHO-UMC criteria for causality.

The search identified a total of 26 cases (27 events) describing occurrence of AMN. In 23 cases the PT Acute macular neuroretinopathy was included. These 23 cases were reported with 24 PTs of Acute macular neuroretinopathy. One literature case PPD had reported events of AMN and PAMM both of which were coded to PT Acute macular neuroretinopathy. The verbatim term PPD codes to the PT Acute macular neuroretinopathy and was included in the search.

Coding errors were identified (and are now pending correction) in the remaining 3 of 26 cases. Two cases had the verbatim Paracentral Acute Middle Maculopathy coded to PT 'Maculopathy' and 1 case had the verbatim Acute Macular Retinopathy coded to 'Maculopathy'.

All 26 cases were from post-market sources, 18 cases were reported from spontaneous sources and 8 (cases PPD were from literature sources.

Twenty of the 26 cases were reported as serious and 21 cases were medically confirmed. None of the cases had a fatal outcome.

Out of the 26 cases, 6 were reported in the UK, 5 were reported in Germany, 3 each were reported in Italy and Netherlands, 2 each were reported in Austria and France, and 1 each was reported in [redacted]

Twenty three out of these 26 cases were included in the previous bi-monthly Summary Safety Reports. The three newly presented cases were PPD PPD.

The cases PPD were found to be duplicates of the cases PPD respectively. The cases PPD were suppressed as the cases contained limited information.

Twenty-three (88.5 %) of the 26 reported cases occurred in females and gender was missing in 2 cases. In 24 cases, the age range was 18 – 35 years, and in the remaining 2 cases the age was not reported. Median age was 21.5 years.

Time to onset was reported as within 1 - 2 days post- vaccination in 18 reports, 3 days post-vaccination in 1 report and 28 days post-vaccination in 1 report. TTO was not reported in 6 cases.

The outcomes for the 27 events were as follows: Not recovered (11), Recovering (7), Ongoing (1), Recovered (1) and Unknown (7).

Relevant Medical/ocular history was reported in 7 of the 26 cases. Of these, the relevant medical/ocular history included Acute zonal occult outer retinopathy (AZOOR) (1), Hypothyroidism (1), Eye swelling (1), Juvenile idiopathic arthritis (JIA) (1), iritis (1), and Anterior chamber inflammation (1).

Two cases had co-reported events of influenza-like symptoms.

This review identified concomitant use of contraceptives in 11 of the 26 reports. Other reported concomitant medications included Isotretinoin, levocetirizine, Prednisolone, Methotrexate, sulfasalazine, topical steroids.

In 13 of the 26 cases the information was limited, with no reported diagnostic criteria, ocular/medical history, concomitant medications, ophthalmic assessments/investigations to have a meaningful assessment of these cases.

AstraZeneca assessed the causality of the 26 cases utilizing the WHO-UMC criteria. Causality of 20 out of the 26 cases were assessed as ‘possible’, 5 as ‘unassessable’, and 1 as ‘probable.’

For 9 of the 20 cases with Possible causality, this assessment was based solely on the reasonable TTO parameter, and no information was available on assessments of other etiologies, or the vaccinees’ medical history, risk factors, comorbidities, or concomitant medications. For the remaining 11 cases with Possible causality, this assessment was based on a reasonable TTO, and potential risk factors, of which oral contraceptives use was reported in 10 cases and 1 case had a 3 year ocular history of AZOOR.

For 4 of the 5 cases with Unassessable causality, this assessment was based on the unavailability of TTO, assessments of other etiologies, or the vaccinees’ medical history, risk factors, comorbidities, or concomitant medications. For the remaining 1 case with Unassessable causality, this assessment was based on the unavailability of TTO, but with an existing potential risk factor of oral contraceptive use and co-reported event of influenza-like illness.

For the 1 case with Probable causality, this assessment was based on the reasonable TTO parameter, available ocular examination/investigation, retinal images, and that the vaccinee had no pre-existing medical history and was not taking any medication.

In the assessment report for the 8th Summary Safety Update PRAC had requested that the ophthalmology panel should comment both on causality and diagnosis for each AMN/PAMM case. The ophthalmology panellists have reviewed all 26 reports of AMN and offered opinion on the diagnostic likelihood of AMN and WHO-UMC causality, included in Table 21 below. For 13 of the 26 cases with 'Possible' causality, this assessment was based solely on the reasonable TTO parameter, no available retinal images/ocular investigation. The cases contained insufficient information on assessments of other etiologies, or the vaccinees' medical history, risk factors, comorbidities, or concomitant medications but in 6 cases oral contraceptive use was reported. For 8 of the 26 cases with 'Probable' causality, this assessment was based on a reasonable TTO, available retinal image results, and potential risk factors of which oral contraceptives use was reported in 6 cases. For 3 of the 26 cases with 'Unassessable' causality, this assessment was based on the unavailability of TTO, assessments of other etiologies, or the vaccinees' medical history, risk factors, comorbidities, or concomitant medications. For 1 literature case (PPD) of the 29 cases, the causality was assessed as 'Unlikely as the panelist diagnosed the case as an 'alternative diagnosis likely' and not a case of AMN. The causality on case PPD was not provided as the case indicated a diagnosis of PPD instead of AMN.

AstraZeneca has received additional information for case# PPD from the author of this published case report. The author confirmed that the patient developed headache and fever prior to the event. No additional information had been received from the authors of the remaining 5 literature reports.

The 26 cases of Acute macular outer retinopathy are summarized in Table 21 below.

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD / Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	1	PPD	Recovering	Vaccinee reported macular rash and developed PPD central visual scotomas 24 to 48 hours post-vaccination. Amsler grid testing showed PPD scotomas. OCT showed evidence of bilateral acute macular neuro-retinopathy. Automated perimetry, OCT, OCT-angiography were performed, but results are not provided. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/Probable (based on the available retinal image information) **AstraZeneca (AZ) comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. Information regarding results of fundoscopic examination and brain imaging not provided. Macular rash suggestive of an allergic- type reaction, but no further information has been provided.
PPD / Acute macular neuroretinopathy	PPD	PPD	2		Not Recovered	Two days after vaccination, vaccinee experienced acute macular outer retinopathy and on unknown date experienced vision blurred, myalgia, headache

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD)/ Non serious						and pyrexia. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the events acute macular outer retinopathy and vision blurred could be related. No information on ophthalmic examination or history. Medical history and concomitant medications not provided. The case contained limited information.
PPD / Acute macular neuroretinopathy (PPD) PPD	PPD	PPD	2	PPD	Not Recovered	Vaccinee experienced acute macular outer retinopathy 2 days after vaccination. The event was considered serious. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available)

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD / Non serious						**AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by PPD intake. In addition, no information on exams or results provided.
PPD / Acute macular neuroretinopathy PPD) Serious	PPD	PPD	2	PPD	Not Recovered	Two days post-vaccination vaccinee experienced acute unilateral macular neuro-retinopathy. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association, However, the case is confounded by intake of PPD. No information on eye examinations provided.
PPD / Acute macular neuroretinopathy	PPD	PPD	1	Not Reported	Not Recovered	On the day of vaccination, the vaccinee experienced visual impairment, scotomas on PPD eye; also experienced acute macular neuro-

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD)/ Serious						retinopathy in the PPD eye, fever, and cephalea (headache). **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No information on fundus or orbital examination results. Medical history not provided.
PPD / Acute macular neuroretinopathy PPD)/ Non serious	PPD	PPD	Unk	Not Reported	Recovering	Vaccinee developed acute macular neuro-retinopathy on an unknown date. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Insufficient information to confirm AMN/Unassessable (as retinal image/investigation not available and very limited information) **AZ comment**: Based on WHO-UMC

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						classification, the causality assessment is Unassessable due to limited information and no information on time to onset. No information provided on medical history or eye/diagnostic examinations.
PPD / Acute macular neuroretinopathy (PPD)/ Serious	PPD	PPD	2	PPD	Not Recovered	Two days following vaccination vaccinee experienced central absolute scotomas in PPD with diagnosis of acute macular outer retinopathy and scintillating scotoma. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment:** Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case confounded by use of PPD . No ophthalmic investigation (eg, optical coherence tomography, OCT) data presented. No information on ophthalmic history or Medical history were provided.

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD / Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	2	PPD	Not Recovered	On the same day post vaccine, the vaccinee had malaise and two days later experienced acute macular outer retinopathy and visual impairment. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the events acute macular outer retinopathy and visual impairment could be related. Confounded by intake of PPD . No information on ophthalmic examination or history. Medical history not provided.
PPD / Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	1		Recovering	One day post vaccine, the vaccinee experienced acute macular outer retinopathy in PPD . **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality:** Possibly a case

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by intake of PPD . No information on ophthalmic examination or history. Medical history and concomitant medications not provided.
PPD (Literature case: Mambretti et al 2021)/ Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	2	PPD	Unknown	Vaccinee experienced influenza like illness including pyrexia on the first post vaccination day. 2 days after the vaccine, experienced sudden onset of paracentral scotoma in PPD eye. Best-corrected visual acuity (BCVA) was 20/20 in the affected eye with no signs of inflammation. OCT of PPD eye was consistent with acute macular outer retinopathy. FA and ICGA did not reveal any additional pathologic changes. Vaccinee had been on long-term PPD with no history of thromboembolic events. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						of AMN/Probable (based on the available retinal image information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by long-term use of PPD and alternate etiology of co-reported event influenza like illness. Medical history not provided.
PPD (Literature case: Mambretti et al 2021)/ Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	2	PPD	Unknown	Vaccinee experienced sudden onset of scotoma in PPD eye 2 days after the first dose of vaccine, and a day of pyrexia following vaccination. Best-corrected visual acuity (BCVA) in RE was 20/20 with no signs of inflammation. Fundus examination of RE revealed barely visible PPD . Multimodal retinal imaging of PPD eye including OCT of PPD eye was suggestive of acute macular outer retinopathy. Flourescein angiography (FA) and indocyanine green angiography (ICGA) were unremarkable. Blood tests showed reduced neutrophil counts, slightly decreased platelet count with very mild thrombocytopenia. D-dimer and fibrinogen were within limits and serology for COVID-19 was negative. **Ophthalmology Panelist comment on**

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						diagnosis/WHO-UMC Causality: Definite case of AMN/Probable (based on the available retinal image information) **AZ comment on causality**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by intake PPD for PPD years. Medical history not provided.
PPD (Literature case: Book et al 2021/ Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	3	PPD	Unknown	Vaccinee experienced PPD paracentral scotomas were reported 3 days after receiving the first dose of vaccination. Ophthalmoscopy showed PPD that were easily visible on infrared reflectance imaging and matched with PPD on optical coherence tomography. Microperimetry demonstrated PPD scotomas corresponding to these PPD. Bilateral acute macular neuroretinopathy was diagnosed. No additional ocular, orbital, and cerebral pathologies were found on clinical ophthalmic, neurological, and imaging workups, including magnetic resonance angiography. Apart

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						from birth control use, the patient's medical history was unremarkable. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/Probable (based on the available microperimetry information) **AZ comment on causality**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by intake PPD of unknown duration and start time. No information on ophthalmic examination or history. Medical history and concomitant medications not provided.
PPD / Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	1	Not Reported	Unknown	Vaccinee experienced acute macular outer retinopathy one day post vaccine. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality:** Insufficient information to confirm AMN/ Possible (as retinal image/investigation not available and insufficient information)

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						AZ comment on causality: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, this case contains limited information. No information on ophthalmic examination or history. Medical history and concomitant medications not provided.
PPD / Acute macular neuroretinopathy PPD)/ Non Serious	PPD	Unk	2	Not Reported	Not Recovered	Vaccinee experienced Acute macular retinopathy 2 days post vaccination . On an unknown date the vaccinee also developed headache, nausea, myalgia and dizziness. The events were reported to be not recovered and were considered as non-serious. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality:** Insufficient information to confirm AMN/Unassessable (as retinal image/investigation not available and very limited information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No information on ophthalmic examination or history. Medical history

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						and concomitant medications not provided.
PPD / Acute macular neuroretinopathy PPD)/ Serious	PPD	PPD	28	PPD	Not Recovered	Vaccinee experienced acute zonal occult outer retinopathy (PT AMN) 28 days after vaccination. The vaccinee has an ocular history of PPD and medical history of hypothyroidism. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Alternative diagnosis likely/Not assessed by panelist as it is a case of PPD with history of PPD **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the event is confounded by the alternate etiology of prior PPD and medical history of hypothyroidism. No information on ophthalmic examination or investigation. Prior medications not provided.

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD / Acute macular neuroretinopathy (PPD)/ Non Serious	PPD	PPD	1	Not Reported	Not Recovered	Vaccinee experienced acute macular neuroretinopathy PPD 1 day post vaccination. The events were ongoing and case was considered non-serious. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No information on ophthalmic examination, history or investigation. Medical history and concomitant medications were not provided.
PPD / Acute macular neuroretinopathy PPD)/Serious	PPD	Unk/ PPI	Unk	Not Reported	Recovering	Vaccinee experienced acute macular neuroretinopathy, lethargy, malaise, myalgia and pyrexia following vaccination. The events were improving and the case was considered serious. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Insufficient

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						information to confirm AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Unassessable due to lack of information, including time to onset. The date of the vaccination and age of the patient was not reported. No information on ophthalmic examination, history or investigation. Medical history and concomitant medications were not provided
PPD / Acute macular neuroretinopathy (PPD)/ Serious	PPD	PPD /Unk	Unk	Not Reported	Unknown	Vaccinee experienced acute macular neuroretinopathy and PPD following vaccination. The outcome of the events were unknown and the case was considered serious. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Insufficient information to confirm AMN/Unassessable (as retinal image/investigation not available and very limited information) **AZ comment**: Based on WHO-UMC

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						classification, the causality assessment is Unassessable due to lack of information, including time to onset. The date of the vaccination was not reported. No information on ophthalmic examination, history or investigation. Medical history and concomitant medications were not provided.
PPD (Literature case: Drüke et al 2021/ Acute macular neuroretinopathy (PPD)/ Serious	PPD	PPD	1	PPD	Recovering	Vaccinee experienced headache and neck pain on the same day post vaccine. The case was diagnosed as Acute macular neuroretinopathy. Medical history was PPD . Had anterior chamber inflammation six weeks earlier with left knee joint swelling treated with intraarticular steroid three weeks prior to the vaccination. Concomitant medications reported included PPD , PPD . **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Definite case of AMN/Probable (based on the available retinal image information)

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						AZ comment: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by PPD and history PPD and uveitis. PPD is confounding for iritis which could be related to headache.
PPD (Literature case: Michel et al 2021)/ Acute macular neuroretinopathy PPD)/ Serious (duplicate of the suppressed case# PPD)	PPD	PPD	2	PPD	Recovered	Vaccinee experienced sudden onset of four central scotomas (acute macular outer retinopathy) in PPD eye 2 days after the first dose of vaccine. Pyrexia and chills was also reported few hours after vaccination. BCVA was 20/20 OU; anterior segment and fundus examination was normal in both eyes. Near infrared imaging revealed a PPD and SD-OCT showed PPD consistent with AMN. Subtle macular PPD was observed in the PPD eye. Metroversion Visual field 10-2 testing confirmed paracentral scotoma in PPD eye. Initial labs revealed high-level C-reactive protein, leukopenia but platelet, coagulation screening, prothrombin time and activated partial thromboplastin was normal. PPD tested negative for

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						anti-nuclear and antiphospholipid antibodies. 4 days after initial presentation, SD-OCT showed PPD A new blood test showed normalization of the cell blood count and of the C-Reactive protein. 6 weeks after initial presentation, Metroversion Visual field 10-2 testing showed improvement and SD-OCT showed PPD .. Patient denied any relevant medical or family history. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/Probable (based on the available retinal image information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case is confounded by intake PPD for PPD years.
PPD (Literature case: Girbardt et al 2021/	PPD	PPD	3	PPD	Unknown	Vaccinee experienced a circumscribed scotoma in PPD eye 3 days after the first dose of vaccine. BCVA was 1.0 (decimal) OU; anterior segment

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
Acute macular neuroretinopathy PPD)/ Serious						and fundus examination was unremarkable in both eyes. Automated-computed perimetry showed small, round, centrally located circumscribed scotomas in PPD . Infrared images and en-face OCT images of the level of the ellipsoid zone showed PPD . B-scan OCT revealed corresponding subtle PPD that were not detectable upon ophthalmoscopic examination. OCTA showed normal perfusion in both eyes. Magnetic resonance angiography (MRA) ruled out signs of sinus venous thrombosis or cerebral vasculitis. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Definite case of AMN /Probable (based on the available retinal image information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Probable. Association between the event and COVID-19 VACCINE ASTRAZENECA cannot be ruled out.

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
PPD / Serious	PPD	PPD	2	Medical history Not Reported, unspecified medication	Not Recovered	One day after vaccination, the vaccinee experienced fever and 2 days post vaccination developed paracentral acute middle maculopathy (PT: Maculopathy). **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No information provided on medical/ocular history, concomitant medication, ophthalmic assessment/diagnostic/investigations.
PPD /Non-Serious	PPD	PPD	2	Not Reported	Not Recovered	Two days after vaccination, the vaccinee experienced paracentral acute middle maculopathy (PT: Maculopathy).

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible. However, the case contained limited information. No information provided on medical/ocular history, concomitant medication, ophthalmic assessment/diagnostic/investigations.
PPD / Serious	PPD	PPD	1	Not Reported	Not Recovered	One day after vaccination, the vaccinee experienced acute macular retinopathy (PT: Retinopathy). **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Possibly a case of AMN/ Possible (as retinal image/investigation not available and insufficient information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No information

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						provided on medical/ocular history, concomitant medication, ophthalmic assessment/diagnostic/investigations.
PPD (Literature case: Bøhler et al 2021)/ Serious	PPD	PPD	Unk	PPD	Unkown	The vaccinee experienced influenza like illness on the same day of first dose of vaccination which resolved 2 days later but a PPD paracentral scotoma. PPD was also reported. BCVA was 20/20 OU, perimetry of PPD eye showed modest paracentral scotoma in the PPD . IOP was normal in both eye and there was no sign of intraocular inflammation. Fundoscopy of PPD eye revealed a PPD and SS OCT was consistent acute macular neuroretinopathy (PT: Retinopathy) which demonstrated slight PPD SS-OCT angiography indicated subtle PPD There was no evidence of VITT; laboratory work-up showed a normal complete blood count, negative C-reactive protein

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						and absence of antibodies to platelet factor 4-polyanion complexes. **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Definite case of AMN /Probable (based on the available retinal image information) **AZ comment**: Based on WHO-UMC classification, the causality assessment is Unassessable due to lack of information, including time to onset. The ocular events are confounded by history of PPD intake and by the co-reported event influenza like illness
PPD (Literature case: Vinzamuri et al 2021)/ Serious	PPD	PPD	Unk	Not Reported	Recovering	Vaccinee experienced bilateral PAMM (PT: Maculopathy) and AMN (PT: Retinopathy) following vaccination. On examination VA was 6/6 in PPD, anterior segment was unremarkable and fundus was normal. MRI, MR-angiography, Amsler grid, Visual-evoked potential (VEP) were normal. The OCT macula revealed normal foveal contour with PPD There were PPD

Table 21 Cases of Acute macular outer retinopathy associated with use of COVID-19 VACCINE ASTRAZENECA

Case ID/ PT (Verbatim)/Case seriousness	Country	Age (years) / Sex	TTO (days)	Relevant Medical History, Concurrent Medical conditions, Risk factors, Concomitant Medications	Event Outcome	Comments
						PPD All these changes were localized to the area between the PPD **Ophthalmology Panelist comment on diagnosis/WHO-UMC Causality**: Alternative diagnosis likely/Unlikely **AZ comment**: The date of the vaccination and TTO was not reported. Medical history and concomitant medications were not provided. The case contained insufficient information. **AstraZeneca (AZ) WHO-UMC causality**: Unassessable

AMN, Acute Macular Neuro-retinopathy, AZOOR Acute Occult Outer Retinopathy, BCVA Best-Corrected Visual Acuity, B-Scan Brightness Scan, EZ Ellipsoid Zone, F, Female, FA Fluorescein Angiography, ICGA Indocyanine Green Angiography, IOP Intraocular Pressure, IS Inner Segment, IZ Interdigitization Zone, JIA Juvenile Idiopathic Arthritis, M, Male, OCTA, Optical Coherence Tomography Angiography, ONL Outer Nuclear Layers, OPL Outer Plexiform Layer, OS Outer Segment, OU Both Eyes, PAMM Paracentral Acute Middle Maculopathy, PT Preferred Term, SD-OCT Spectral Domain Optical Coherence Tomography, SS-OCT Swept Source Optical Coherence Tomography TTO Time to Onset; UK, United Kingdom; Unk, Unknown; UMC Uppsala Monitoring Centre, VA Visual Acuity, VEP Visual-Evoked Potential, VITT Vaccine-Induced Immune Thrombotic Thrombocytopenia, WHO World Health Organization

Observed versus Expected Analysis

It has been reported that AMN occurs rarely in the general population but is becoming more frequently diagnosed as diagnostic and imaging procedures improve. Based on estimates from a comprehensive case review of 101 reported cases of AMN reported worldwide from 1974 through 2014 (Bhavsar et al 2016), a conservative estimate of the prevalence of AMOR is less than 1/1,000,000. A more precise estimate of the prevalence of AMN/AMOR in the general population has not been identified in the literature.

Through 28 December 2021, approximately 118 million COVID-19 VACCINE ASTRAZENECA have been administered in the UK and EU with 1.6 billion COVID-19 VACCINE ASTRAZENECA vaccines administered globally. Based on these estimates, the expected number of AMN/AMOR reported with COVID-19 VACCINE ASTRAZENECA is approximately between 118 and 1600. Using this estimate, the cumulative observed number of cases of AMN (n = 26) is less than the expected number of cases in the general population and thus is not reflective of an increased reporting of AMN/AMOR following vaccination with COVID-19 VACCINE ASTRAZENECA.

Literature

An updated cumulative search of the literature was conducted through 28 December 2021 to identify any relevant literature, including mechanism of action of AMN with COVID-19 Vaccines using Embase, Insight Meme and Pubmed. No new literature was identified in addition to what was provided in the last review in the 8th safety summary report (Review period: 01 October 2021 – 30 November 2021).

Summary

Bhavsar et al 2016 reported that AMN tended to occur in young, white, and female. The risk factors noted in the article were non-specific flu-like illness or fever (includes influenza, upper respiratory infection, sinusitis, enteritis, pharyngitis, and bronchitis), use of oral contraceptives, epinephrine or ephedrine, severe bodily/non-ocular trauma, systemic shock, dehydration and hypovolemia.

Ryan et al 2019 described the microvascular ischemia of the choriocapillaris as a leading theory for the pathophysiology. Vasoconstriction, decreased blood flow in choriocapillaris followed by hypoxic insult to the middle retina and then the outer retina and other mechanisms of hyperviscosity from leukocytosis, increased capillary permeability, endothelial dysfunction and coagulopathy, platelet destruction, immune complex deposition, and consumptive coagulopathy.

The demographics of the 26 cases identified through this updated review of the global safety database were consistent with those reported in the general population, with 23 cases in females and the age range of 18-35 years and the most reported association of the intake of oral contraceptives (Bhavsar et al 2016).

The majority of the case reports analysed in this review were confounded by alternative aetiologies, underlying medical conditions and/or concomitant medications such as oral contraceptives and the remaining had limited information to sufficiently assess the cases. Ocular examination and investigations were provided in only 10 of the cases. Twelve of the 26 cases that were assessed as 'possible' and 1 as 'unassessable' to be related had confounding/risk factors and 11 were on oral contraceptives. Nine of the 26 cases that were assessed as 'possible' to be related had limited information but the time to onset was reported. The remaining four cases that were assessed as causally 'unassessable' did not contain the time to onset in addition to the limited information. There was 1 case which was assessed as 'probable' applying the WHO-UMC criteria causality.

Review by the ophthalmology panel determined the diagnosis as 'definite cases of AMN' in 4 cases, 'possible case AMN' in 15 cases, 'insufficient information to confirm AMN' in 5 cases, and 'alternative diagnosis likely' in 2 cases. The expert panel also provided their causality assessment utilizing the WHO-UMC criteria. Thirteen of the 26 cases were assessed by the panel as 'possible' related in which 5 were on oral contraceptives. Eight of the 26 cases were assessed by the panel as 'probable' as these cases contained information on retinal images although the time to onset in 2 cases was unknown and in 6 cases patients were on oral contraceptives. Three of the 26 were assessed by the panel as 'unassessable' as these cases did not contain sufficient information to establish a causality. One case PPD was assessed as 'Unlikely' related as in the opinion of the panelist the case was not AMN. In the remaining 1 case (PPD) the panel did not provide a causality as this was assessed as a case of PPD and not AMN.

It has been reported that AMN occurs rarely in the general population, but is coming more frequently diagnosed as diagnostic and imaging procedures improve (Bhavsar et al 2016). However, proper and relevant past and current ophthalmic history/examination/investigation, medical history or concomitant medications were not reported in most of the cases. The cumulative observed number of cases of AMN (n = 26) is less than the expected number of cases in the general population and thus is not reflective of an increased reporting of AMN/AMOR following vaccination with COVID-19 VACCINE ASTRAZENECA.

Conclusion

The conclusions of this updated review of reports of AMN with COVID-19 VACCINE ASTRAZENECA are consistent with those provided in AstraZeneca's responses to PRAC's previous request regarding AMN/AMOR. Based on the available data as of 28 December 2021, AstraZeneca considers that there is insufficient evidence to establish a causal relationship between COVID-19 VACCINE ASTRAZENECA and AMN. No update to the product information or RMP is warranted. AstraZeneca will continue to closely monitor safety information for AMN from all available sources as part of the routine safety surveillance.

15.2.2 Adult-onset Still's disease

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021:

"The MAH is requested to comment on the signal from WHO-UMC on Adult-Onset Still's disease (AOSD) and to provide a cumulative review of cases reported with Vaxzevria. A discussion on the need to update the PI should be included."

AstraZeneca's response to this request is provided below.

Review of cases

A cumulative search of the AstraZeneca Global Patient Safety Database (data cut-off: 28 December 2021) was conducted for AE reports of Still's disease in association with the use of COVID-19 VACCINE ASTRAZENECA. The search included the following PT (MedDRA version 24.1): Still's disease.

In addition, a search was conducted in the AstraZeneca Clinical database for adverse event (AE) reports of Still's disease following use of COVID-19 VACCINE ASTRAZENECA reported from clinical studies (data cut-off of 07 December 2020 for the Oxford pooled studies and 30 July 2021 for Study D8110C00001). The search utilized Medical Dictionary for Regulatory Activities (MedDRA version 23.1) with the following PT: Still's disease. There were no case reports of Still's Disease from the Oxford pooled studies (COV001, COV002, COV003, and COV005), and no cases in the United States (US) study (D8110C00001).

The cumulative search of the AstraZeneca Global Patient Safety Database retrieved 24 cases, each reporting an event with a PT of Still's disease. One case (Case ID: PPD) had a suspected AE coding error, which described a subject with "PPD ", and no evidence supporting association with Still's disease and will therefore not be included. The discussion will focus on the remaining 23 cases.

All 23 cases were from spontaneous reports (20 regulatory reports, 2 consumer reports, and 1 literature report) and all events were considered serious. 18 of the vaccinees was hospitalized after administration of the AstraZeneca COVID-19 vaccine. In addition, out of the 24 reports 5 (20.8 %) cases were considered life threatening. Disability was also reported 1 (4.2 %) in of the case reports. 13 (54.2 %) reported hospitalization, and the remaining 5 (20.8 %) reports were medically important. Of the 23 cases, 11 (46%) were medically confirmed.

Of the 23 cases, 6 were from Italy; 6 were from the United Kingdom (UK); 4 cases were from Germany; and 1 case each came from [redacted]. Ethnicity was not reported in 22 cases and the remaining 1 case involved an [redacted] patient.

Of the 23 cases, 13 were male and 10 were female. The median age was 52 years (range from 25 to 66 years): 20 cases had ages between 25 to < 65 years; in 2 cases the age was 65 years; and, in the remaining 1 case the age was 66 years.

The pathogenesis of AOSD is not completely known, it is suggested that a combination of external factors such as infections and a genetic susceptibility lead to an activation of an innate immune response with cytokine overproduction (Sfriso et al 2018). The time to onset (TTO) of the event of Still's disease was reported in 19 cases and ranged from < 1 day to 72 days; and, in the remaining in 4 cases TTO was not reported. Of the 19 cases with reported TTOs, 17 had an AE onset ≤ 23 days; the remaining 2 cases had TTOs of 56 and 72 days, respectively. In addition, of the 19 cases with reported TTOs, 18 reported AE onset after the first dose of COVID-19 VACCINE ASTRAZENECA and 1 case reported AE onset after the second dose. For the rest (14), the dose information is missing.

Event outcomes at the time of reporting were as follows: 9 events were not recovered, 8 events were recovering, 2 events were recovered with sequelae, and the outcome for the remaining 4 events was unknown. No fatal outcomes were reported.

AstraZeneca assigned WHO-UMC causality for all 23 cases using a risk window within 42 days. Out of 23 cases, a risk assessment of unassessable was provided for two cases (PPD) due to insufficient information to ascertain latency, clinical course, relevant investigations, medical history and concomitant medications. In two cases (PPD) the risk assessment was considered as unlikely as the TTO was either too short (same day onset) or too long (72 days) to be temporarily plausible to vaccine administration. Although the TTO was reasonable in the remaining 19 cases, there was insufficient information on medical history or concomitant medication or action taken with concomitant medication or insufficient work up of other etiologies (such as infectious, auto-immune conditions and neoplasms).

Of the 23 cases reviewed, 9 had possible confounders for Still's disease (eg, medical history of juvenile rheumatoid arthritis, recent hepatitis B virus vaccination, pre-existing Still's disease, arthritis, infective endocarditis, severe COVID-19 infection). One of the 8 cases (Case ID PPD) was from a literature source and is discussed in the literature section here below. The remaining 14 cases had insufficient information, which precluded a proper causality assessment (they lacked information such as [and was not limited to] medical history, concomitant medications, clinical presentation and progress, laboratory and imaging results, and confirmatory diagnostic work-ups).

Literature

A search of Embase and InsightMeme databases was conducted for literature articles on 'Still's disease' following the use of COVID-19 VACCINE ASTRAZENECA, and other COVID-19 vaccines. The literature search yielded 1 article:

The article (Jeon et al 2021) described a case of a PPD -year-old PPD patient from PPD (Case ID PPD) with Still's disease who experienced a flare after a ChAdOx1 nCoV 19 vaccination, and was considered to be relevant for discussion. The patient presented a febrile sensation for 2 days and also complained of arthralgia, myalgia, sore throat, pleuritic chest pain, and a macular salmon-pink rash PPD . Reportedly, patient was diagnosed

with Still's disease at the age of PPD years and was doing well without a flare for PPD years. PPD received the first dose of ChAdOx1 nCoV-19 vaccine 9 days prior to the date of the report. The patient commenced treatment with PPD and empirical antibiotics, however, PPD pleuritic chest pain aggravated. On the 7th day of hospitalization (HD), the dose of PPD was increased to control the flare of Still's disease. High-dose glucocorticoid therapy was temporarily effective in improving fever, chest pain, arthralgia, and rash for approximately 4 days. PPD was further treated with PPD pulse therapy for 3 days followed by PPD. Antibiotic treatment was discontinued. This treatment approach led to transient improvement in the patient symptoms and laboratory findings. However, right-sided pleuritic chest pain and fever recurred with the macular rash spreading to PPD extremities on HD 25. Empirical antibiotics were re administered, and the dose of PPD was reduced; however, the symptoms had failed to improve. Blood and pleural fluid culture was negative for infectious conditions. As a treatment of the refractory Still's disease, PPD was administrated on HD 32 along with PPD, which significantly improved the patient symptoms and laboratory findings. The patient was discharged 7 days later. The improvement was maintained without symptoms for two months with PPD. At the time of reporting, the event was improving.

AstraZeneca Comment: Jeon et al 2021 classified this case as "major" based on Yamaguchi criteria (Yamaguchi et al 1992) for the diagnosis of Adult-onset Still's Disease (AOSD). However, patient was reported to have medical history of PPD and was on PPD maintenance therapy. A flare up was reported to have been experienced 9 days after COVID-19 vaccination. There was no information on any action taken for the immune modifiers (PPD) in the immediate peri and post vaccination period. There was also insufficient information on vaccine reactogenicity symptoms, especially in the backdrop of flare-up latency of 9 days which do not coincide with the usual onset of innate immunity and chemokines (IL-2, IL-6 and so on). Many remissions and flare up to high dose steroids, PPD led to diagnosis of resistant Still's disease which responded well to PPD and may suggest a IgG response to an already existing PPD etiopathogenesis. Due to insufficient information on action taken for the immune modifiers (PPD) in the immediate peri and post vaccination period and correlation with vaccine reactogenicity in the backdrop of PPD maintenance therapy, a comprehensive medical assessment of flare up of AE is not possible. Also, recurrence at PPD years of age aligns with the bimodal age distribution. This is in line with the reporter's conclusion that 'The causal relationship between COVID-19 vaccination and flare cannot be clarified in this case.'

Summary

In summary, all 24 cases pertaining to searched term of Adult onset Still's disease were considered serious which is expected as Adult onset Still's disease is considered to be a medically significant event. No fatal event was reported. One case had a suspected AE coding

error and was excluded from further review. There was no predisposition with respect to gender distribution. The median age of 52 years is considered to be in line with known bimodal distribution of AOSD in the scientific literature (Efthimiou et al 2021). Based on reasonable TTO, 20 cases are assessed as possible however there was insufficient information on medical history or concomitant medication or action taken with concomitant medication or insufficient work up of other etiologies (such as infectious, auto-immune conditions and neoplasms) precluding comprehensive causal assessment. Sufficient case details for comprehensive causality assessment was identified only in 39% of cases (9 out of 23) and in all cases confounders were seen such as medical history of juvenile rheumatoid arthritis, recent hepatitis B virus vaccination, pre-existing Still's disease, arthritis, infective endocarditis, severe COVID-19 infection. Thus, among the 23 cases received and analysed for Still's disease by AstraZeneca, the vast majority had limited information or confounders were identified.

Conclusion

Based on available cumulative data up until 28 December 2021, AstraZeneca considers that there is no evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and Still's disease. No update to the core product information or RMP is warranted.

AstraZeneca will continue to monitor safety data of Still's disease from all available sources as part of the routine safety surveillance.

15.2.3 Autoimmune hepatitis

Request

AstraZeneca received the following request from PRAC in the Assessment Report (AR) for the 7th SSR (review period: 01 August 2021 – 30 September 2021):

Autoimmune hepatitis: The MAH is requested to provide a cumulative review of cases of autoimmune hepatitis from spontaneous reporting and from the literature. The review should include a detailed discussion of well-described cases with plausible TTO. The narrative of cases should be also provided."

AstraZeneca's response to this request is provided below.

Review of cases

A cumulative search of the AstraZeneca Global Patient Safety Database (data cut-off: 28 December 2021) was conducted on 29 December 2021 for adverse event reports of Autoimmune hepatitis in association with the use of AZD1222. The search strategy used PTs of Autoimmune hepatitis; Immune-mediated hepatitis using MedDRA (version 24.1).

The search identified a total of 33 cases of which 30 (91%) were from spontaneous source, 2 (6%) from literature and 1 (3%) from non-interventional study. Of these 33 cases, 20 were females, 11 males and gender unknown in 02 cases. There were 14 (42%) case reports from adult (18 - 64 years of age) vaccinees, 16 (49%) from elderly (≥65 years of age) vaccinees and age was unknown in 03 (9%) vaccinees. Most of the cases were from the United Kingdom (14 cases [42%]), followed by Australia, Austria, Brazil, Germany with 03 (9%) cases each, France, India with 02 (6%) cases each and then [redacted] with 01 (3%) case each.

These 33 cases reported 33 events of which 30 (91%) were reported as serious and 18 (55%) medically confirmed. These 30 AEs were considered serious due to the AE being considered as medially important (16), the AE was reported to have resulted in disability (04), required hospitalization (15), was life threatening (05), and/or resulted in death (03). Cases may have met more than one criterion for seriousness.

The event outcomes at the time of reporting were as follows: 12 events (not recovered), 6 events (recovering), 3 events (fatal), 3 events (recovered), 1 event (recovered with sequelae) and 8 events unknown. The count of reported adverse events by preferred terms include Autoimmune hepatitis (29) and Immune-mediated hepatitis (04).

Out of the 33 cases, 10 were reported after 1st dose, and 09 after 2nd dose. The time to onset (TTO) of the event of autoimmune hepatitis (AiH) was reported in 20 cases and ranged from < 1 day to 123 days of which 06 cases were reported after the first dose and 06 cases after the second dose. Of the 20 cases with reported TTOs, 13 had an AE onset ≤ 21 days and the remaining 07 cases had TTOs of >21 days. Refer to Appendix 20 for case narratives, assessment and WHO-UMC causality for all these 33 cases.

AstraZeneca assigned WHO-UMC causality for all 33 cases using a risk window of 42 days. Out of 33 cases, 01 was unlikely (TTO of same day which was considered too short to consider temporally plausible), 17 were unclassified (limited information such as on TTO, medical history, concomitant medications, and laboratory results for proper assessment), 14 were possible (TTO was reasonable but had limited information on etiological, diagnostic work-up, medical history, concomitant medications and laboratory results), and 01 case was assessed as probable (PPD, Rela et al 2021) but had limited information for further analysis which was described in the literature section below.

Literature

A cumulative literature search of the databases in Embase, InsightMeme, and PubMed published through 28 December 2021 was conducted to review the occurrence of autoimmune hepatitis association with COVID-19 VACCINE ASTRAZENECA using key terms for COVID-19 vaccines and autoimmune hepatitis.

The search yielded 16 relevant articles which were all case reports. Thirteen were reported for mRNA vaccines (Avci and Abasiyanik 2021, Bril et al 2021, Garrido et al 2021,

Ghielmetti et al 2021, Palla et al 2021, Parry et al 2021, Vuille-Lessard et al 2021, Londoño et al 2021, McShane et al 2021, Rocco et al 2021, Tan et al 2021, Tun et al 2021, Zhou et al 2022, Ventura et al 2021) and one case report, the type of vaccination was not specified (Sidhu et al 2021). Three case reports were reported for viral vector vaccines and are reviewed in detail in the Table 22 below.

Table 22 Summary of literature articles discussing autoimmune hepatitis with COVID-19 vaccines

Authors Type of study Patient demographics	Vaccine type TTO dose number	Signs and symptoms	Investigations[a]	Insufficient information on Etiological workup	Confounders	Author comments
Clayton-Chubb et al 2021 Case report PPD	ChAdOx1 nCoV-19 vaccine 26 days, 1st	Abnormal findings on routine LFTs	ALT – 1774 AST – 633 ALP – 118 GGT – 136 Bilir (T) – 0.99 IgG – 12.8 ANA - 1:1280 Biopsy - IfH, LpI	COVID-19 status Action taken with concomitant medications	1. statin therapy	This case supports the notion of COVID-19 vaccine-triggered autoimmune phenomena irrespective of the vaccine's mechanism of action, though this is the first report of an adenovirus based vaccine precipitating AIH. Similar to the previously described case by Bril et al 2021., causation cannot be definitively proven and it is possible that other factors, including drugs or toxins, may have contributed to the presentation. In this case, however, the patient is a PPD and we feel it is unlikely that other potential aetiologies were missed on history.
	Company comments: *In this patient, reportedly there is no history or previous hepatic disorders. The patient underwent* PPD *2 weeks before and was on medications. Furthermore, the contributory role of concomitant* PPD *and* PPD *could not be ruled out. As the authors state "the causation cannot be definitely proven and it is possible that other factors, including drugs or toxins, may have contributed to the presentation*					
Rela et al 2021- 1 Case report PPD	Covishield 16 days, 1st	anorexia and jaundice	ALT – 1094 AST – 1361 ALP – unk Bili (T) – 19.2 GGT – unk IgG – unk ANA – negative SMA – negative Biopsy – LpI, RoH	COVID-19 status Complete viral markers (other than viral hepatitis),	1. PPD (with past two episodes of jaundice) 2. Diabetes	

Table 22 Summary of literature articles discussing autoimmune hepatitis with COVID-19 vaccines

Authors Type of study Patient demographics	Vaccine type TTO dose number	Signs and symptoms	Investigations[a]	Insufficient information on Etiological workup	Confounders	Author comments
				PPD Type of diabetes		AiH can occur in predisposed individuals where an immune mediated reaction against hepatocytes is triggered by environmental factors. The authors state that the autoimmune reactions after vaccination are rare and occur in less than 0.01% of all those who are vaccinated. It appears that these reactions are due to an immune intolerance to self-antigens combined with a failure of intrinsic homeostatic systems that prevent a promiscuous immune response to these antigens. According to the authors, supposed mechanisms for this reaction include molecular mimicry between the antigenic determinants of the vaccine and human proteins, leading to autoantibody formation. Other theories include, immune complex formations effecting a T lymphocyte imbalance and a bystander activation as a result of an exuberant innate immune response to the adjuvants added to most vaccines. The authors highlight the fact that most previous reports from the literature involve the influenza vaccine. The authors also acknowledged that there were no clear clinical or biochemical features apart from a chronological association to differentiate the patients' vaccine-related autoimmune hepatitis from idiopathic autoimmune hepatitis.
	Company comments: *TTO of 16 days following first dose of vaccination which is reasonable. Patient had* PPD *(with past two episodes of jaundice) with no active infection and this can confound development of possible autoantibodies. ANA and SMA were negative. As per the available case details (histologic findings of LpI with RoH) which was limited, a Simplified Diagnostic Scoring System for 'auto-immune hepatitis' could not be met. There was insufficient information on alkaline phosphatase levels, complete viral markers (other than viral hepatitis), COVID-19 infection status, any evidence of molecular mimicry, and in the background of transient improvement with later worsening with steroids, no response to plasma exchange,* PPD *, a comprehensive causal assessment was not possible.*					
Rela et al 2021- 2 Case report PPD	Covishield 20 days, 1st		ALT – 1025 AST – 1101 ALP – unk Bili (T) – 14.0 GGT – unk IgG – 16.5 ANA – 1:80 Biopsy – LpI	COVID-19 status Complete viral markers (other than viral hepatitis),	none	
	Company comments: *TTO of 20 days following first dose of vaccination which is reasonable. Patient had pre-existing hypothyroidism (non-autoimmune). As per the available case details (Antinuclear ANA titre, IgG levels, histologic findings of*					

Table 22 Summary of literature articles discussing autoimmune hepatitis with COVID-19 vaccines

Authors Type of study Patient demographics	Vaccine type TTO dose number	Signs and symptoms	Investigations[a]	Insufficient information on Etiological workup	Confounders	Author comments
	Lymphoplasmacytic infiltrate with acinar and peri-portal affections, response to steroids, a Simplified Diagnostic Scoring System indicated probable 'AiH'. There was insufficient information on complete viral markers (other than viral hepatitis) and COVID-19 infection status in the backdrop of patient being a healthcare worker. In view of reasonable TTO and available etiological workup (partial viral markers, unremarkable CT scan of liver, non-autoimmune hypothyroidism) a confounder could not be identified. However, based on insufficient information on complete viral markers (other than viral hepatitis), COVID-19 infection status in the backdrop of patient being a healthcare worker and any evidence of molecular mimicry a further comprehensive causal assessment was not possible.					

[a] units for liver enzymes (ALT, AST, GGT, ALP) – U/L; units for IgG – g/L

AIH Autoimmune hepatitis, ALP Alkaline Phosphatase, ALT Alanine Aminotransferase, ANA Antinuclear antibody, AST Aspartate Aminotransferase, ChAdOx1 Chimpanzee Adenovirus, F Female, GGT Gamma Glutamyl Transferase, HBV Hepatitis B virus, Ig Immunoglobulin, IfH Interface hepatitis, INR International normalized ratio, LpI Lymphoplasmacytic infiltrate, LFTs Liver function tests, M Male, RoH Rosetting of hepatocytes, s seconds, TTO Time to onset, ULN Upper limit of normal, x times, y years.

On review of the 17 case reports in 16 articles, 13 were reported for mRNA vaccines, 3 case reports in 2 articles were reported for viral vector vaccines while in the remaining one case report, the type of vaccination was not specified. All the 3 case reports reporting AiH with viral vector vaccines were reported following 1st dose of the vaccination. Although the TTO was reasonable (16 days, 20 days, 26 days) there were insufficient information to confirm autoimmune etiopathogenesis or confounders were identified as discussed in the table above.

The various mechanisms hypothesized were vaccine-triggered autoimmune phenomena, molecular mimicry between the antigenic determinants of the vaccine and human proteins leading to autoantibody formation and possibility of immune complex formations effecting a T lymphocyte imbalance. However, a further exploration of these mechanisms were not identified in these articles. Interestingly, an autoimmune mechanism based on molecular mimicry was evaluated in only one article (out of 16 total articles) which reported AiH with mRNA COVID-19 vaccine (Londoño et al 2021). The authors explored homology between the SARS-CoV-2 spike protein and soluble liver antigen and no homology was found. Thus, based on review till date, a mechanism based on molecular mimicry could not be proven.

Summary

Autoimmune hepatitis is an immune-mediated inflammatory liver disease of uncertain cause. On review of 33 cases from the AstraZeneca Global Patient Safety Database, there was a slight female disposition (65%) which is in-line with known epidemiology of autoimmune hepatitis (Mack et al 2020). Autoimmune hepatitis is considered to be a medically significant event and hence the majority of the reports were considered serious. Three cases (9%) reported fatal outcome, however these cases had insufficient information for a comprehensive assessment such as dose latency, etiological and diagnostic work-up, medical history, and/or concomitant medications. Upon review of all cases, AstraZeneca assessed 1 case as Probable based on WHO-UMC criteria, but had limited information for further analysis.

Following the review of 16 articles from literature, no conclusive mechanism could be determined. All the literature articles with the use of COVID-19 VACCINE ASTRAZENECA comprised of case reports where there was either insufficient information to confirm AiH etiopathogenesis or confounders were identified for AiH. Thereby, no safety concern was identified from the review of relevant literature articles with vast majority of articles concerning mRNA vaccines.

Thus, from the review of the cumulative data, AstraZeneca did not find any evidence of a new or emerging signal regarding autoimmune hepatitis and COVID-19 VACCINE ASTRAZENECA.

Conclusion

Based on available cumulative data up until 28 December 2021, AstraZeneca considers that there is no evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and autoimmune hepatitis. No update to the core product information or RMP is warranted.

AstraZeneca will continue to monitor safety data of autoimmune hepatitis from all available sources as part of the routine safety surveillance.

15.2.4 Blood pressure increased

Request

During the review period, AstraZeneca received the following request from The State Expert Center of the MoH of Ukraine for inclusion in this PSUR:

"The MAH is requested to provide additional data which contain review of all cases of blood pressure increased, including detailed tabulated data and description of the events (age, gender, dose), diagnosis and establishment of causal association, comments regarding possible risk factors and possible mechanisms of blood pressure increase following administration of COVID-19 VACCINE ASTRAZENECA."

AstraZeneca's response to this request is provided below.

Review of Cases

A cumulative search of the AstraZeneca Global Patient Safety Database was conducted through 28 December 2021 for adverse event reports of Blood pressure increased (MedDRA PT) in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified 7213 cases, upon review two cases were identified as duplicates and were removed (7158 spontaneous, 53 non-interventional/post-marketing) (904 serious and 6307 non-serious events) with 7211 adverse events related to Blood Pressure Increased. Of the 7211 cases, 5117 cases were medically confirmed and 2094 were not medically confirmed. Of the 5117 cases, 201 were AE serious due to the AE being considered as medically important (101), the AE resulted in disability (7), AE required hospitalization (85), AE was life threatening (25) and/or the AE resulted in death (9).

There were 4033 reports in females (56%), 3119 – in males (43%), and 59 (1%) of unknown gender. In 3 (<1%) of 7211 cases, the age range was 0 to <18 years, in 5217 cases (72%) the age group was 18 to <65 years, in 1777 cases (25%) the age group was 65+ years and for the remaining 214 cases (3%) the age was missing and not provided.

Time to onset for the events (Table 23) is shown below:

Table 23 TTO Blood Pressure Increased Events Cumulatively through 28 December 2021

Time First Dose To Case Onset	Number of Events	%
00 Under 1 day	5,108	69.9
01 day	467	6.4
02 days	123	1.7
03 days	88	1.2
04 days	60	0.8
05 days	48	0.7
06 days	34	0.5
07 days	38	0.5
08 days	23	0.3
09 days	23	0.3
10 to 15 days	83	1.1
16 to 20 days	41	0.6
21 to 30 days	61	0.8
31 to 40 days	20	0.3
41 to 60 days	31	0.4
61 to 80 days	36	0.5
81 to 100 days	34	0.5
Over 100 to 200 days	20	0.3
Over 200 days to 1 year	4	0.1
Over 1 year	4	0.1
Undefined (missing)	958	13.1

TTO Time To Onset.

For the 7211 cases, the adverse events outcomes were as follows:

Table 24 AE Outcome for Blood Pressure Increased Cases Cumulatively through 28 December 2021

AE Outcome	Number of PTs	Percentage (%)
Died	9	0.1
Not Recovered	603	8.4
Recovered	4,820	66.8
Recovering	981	13.6
Recovered With Sequelae	40	0.6
Unknown	761	10.6

Due to the broad nature of this medical concept along with the volume of cases of blood pressure increased with COVID-19 VACCINE ASTRAZENECA retrieved in the search, WHO UMC causality assessment was not completed for this review.

Fatal Cases:

Out of 7211 cases, 9 cases reported blood pressure increased as a cause of death. Other causes of death included nausea, vomiting, malaise, headache, dizziness, depressed level of consciousness, loss of consciousness, dyspnoea, decreased appetite, cerebellar infarction, brain herniation, hemiparesis, hypoaesthesia, and injection site pain. In 2 cases the cause of death was only blood pressure increased. These 9 cases generally provided limited information on circumstances leading to death, autopsy information, details on concurrent diseases, concomitant medications and detailed etiologic and diagnostic workup. It was not possible to make a conclusive assessment of the causal relationship between fatal outcome and COVID-19 VACCINE ASTRAZENECA.

Of 4860 cases where the AE had resolved or recovered with sequelae, duration was available in 12% (572) of cases. The mean duration was 3 days (range 0 to 88 days). In 82% (471) of the cases the duration was ≤ 3 days.

Serious, medically confirmed cases:

A thorough review of the 201 serious, medically confirmed cases was completed. A tabulation report containing details of these 201 cases of serious, medically confirmed hypertension is available in Appendix 17.

Approximately 64% (129) of the cases reported that were related to blood pressure increased included the risk factors hypertension, age, obesity/overweight and/or diabetes mellitus. Adults over the age of 50 years accounted for approximately 66% of the 201 serious cases and 60% of the total 7211 cases.

Observed vs Expected Analysis

Observed versus expected analysis for overall cases of blood pressure increased is presented in Table 25.

Table 25 Observed Versus Expected Analysis for Blood Pressure Increased

Age group/ Gender	Risk Window	IR [a]	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
Overall (Global)	14	8752.86	291626957	6083	978417.87	0.01 (0.01 - 0.01)	Observed significantly < expected
Overall (Global) including cases with Unknown TTO	14	8752.86	291626957	6993	978417.87	0.01 (0.01 - 0.01)	Observed significantly < expected
Observed Versus Expected Analysis for Hypertension - Serious and medically confirmed only							
Overall (Global)	14	8752.86	291626957	154	978417.87	0 (0 - 0)	Observed significantly < expected
Overall (Global) including cases with Unknown TTO	14	8752.86	291626957	183	978417.87	0 (0 - 0)	Observed significantly < expected

[a] Incidence Rate (IR) Source: Willame et al 2021 [B] Meta-analysis IR from 2010-2013 and 2017-2019 – Hypertension (Narrow)).

CI Confidence Interval; IR Incidence Rate; TTO Time to Onset.

The results of the O/E analysis showed that for the risk window of 14 days, for global cases, and for cases from the UK and EEA for all age stratifications, observed cases were significantly less than expected for this event. This was the case when considering only serious medically confirmed cases, but also all cases.

Literature

Literature Review Search Strategy:

A search of Embase database was undertaken on 19 January 2022 using the following search terms: blood pressure increase and elevated blood pressure. The search yielded 77 articles. No articles elucidating a mechanism of action with regards to AZD1222 to cause increased blood pressure were found. One article with relevant findings is summarised below.

A study by Sanidas et al 2021 investigated the association between hypertension and COVID-19 vaccines (Pfizer, Astra Zeneca or Moderna). Sixty patients between the ages of 50-70 years of age were randomised to receive one dose of COVID-19 vaccine twice within a month. Half of the patients had pre-existing hypertension under medical treatment and the other half were non

hypertensives. Blood pressure measurements were taken both at home and ambulatory blood pressure measurement were taken between the 1st and 30th day after receiving the second dose of COVID-19 vaccine. All patients recorded at some point a substantial hypertensive response for both systolic and diastolic blood pressure after the second dose of vaccine. Hypertensives were older and had higher body mass index. Some hypertensives received additional medications whereas some of the non-hypertensives started life modification changes and systemic blood pressure measurements for a possible diagnosis. The authors concluded COVID-19 vaccinations were associated with short periods of hypertensive response. This was partial and mostly observed in older overweight hypertensives.

AstraZeneca Comment: Limitations of this study were patients' age and high BMI which are risk factors for high blood pressure. No link has been identified between AstraZeneca Covid -19 vaccine and hypertension.

Summary

There were 7211 (904 serious and 6307 non-serious) cumulative cases of 'Blood Pressure Increased' identified. Females accounted for 56% of the cases and males accounted for 43%. Adults over the age of 50 accounted for 60% of the cases. All serious and medically confirmed cases (201) were analysed individually and no signal was detected. Of these 201 cases, 193 cases (96%) occurred after the first dose, 7 cases (3%) occurred after the second dose, and 1 case (1%) occurred after a booster dose. These 201 cases were AE serious due to the AE being considered as medically important (101), the AE resulted in disability (7), the AE required hospitalization (85), the AE was life threatening (25) and/or the AE resulted in death (9). All of these 201 case reports that were received and analysed by AstraZeneca have limited information and/or are confounded by alternative aetiologies including the possibility of a concurrent COVID-19 infection. Approximately 64% (129) of the serious and medically confirmed cases included the risk factors hypertension, age, obesity/overweight and/or diabetes mellitus. In addition to the analysis of the 201 cases, no safety concern was identified from the literature. The O/E analysis for all reported cases of blood pressure increased showed that observed cases occurred significantly less frequently than expected. No mechanism of action was elucidated with regards to AZD1222 to cause increased blood pressure.

Conclusion

Based on available data as of 29 December 2021, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and blood pressure increased. No literature was identified elucidating a mechanism of action with regards to AZD1222 to cause increased blood pressure. No update to the CDS or RMP is

warranted. AstraZeneca will continue to monitor safety information for blood pressure increased from all available sources as part of the routine safety surveillance.

15.2.5 Booster dosing

Request

During the review period, AstraZeneca was asked by the UK MHRA to provide reviews as to the experience with using COVID-19 VACCINE ASTRAZENECA as a booster (3rd dose) within the PSUR(s).

AstraZeneca's response to this request is provided below.

Review of Cases

A search of the AstraZeneca global safety database was conducted to identify any adverse event (AE) reports involving confirmed 3rd 'booster' dose of COVID-19 VACCINE ASTRAZENECA received cumulatively through 04 January 2022. Confirmed booster was defined as any COVID-19 VACCINE ASTRAZENECA AE report where Dose 3 was indicated in the Dose Text field in the AstraZeneca global safety database and where COVID-19 VACCINE ASTRAZENECA was listed as a Suspect or Co-suspect medication.

Cumulatively, through 04 January 2022, a total of 495 reports have been received of confirmed 'booster' dosing involving COVID-19 VACCINE ASTRAZENECA. Of the 495 reports received, 238 (48%) were serious and 114 (23%) were medically confirmed. The majority of the reports (373, 75%) originated from the United Kingdom with the remaining reports originating from Brazil (56), Philippines (11), Portugal (9), Mexico (7), Argentina (6), Costa Rica and Thailand (4 each), Chile, Malta and Poland (3 each), Columbia, France, and India (2 each), [redacted] (1 each). COVID-19 VACCINE ASTRAZENECA is not approved in the United States (US). However, the case from the [redacted] involved consumer from the [redacted] who advised they had read about a report of Intracranial pressure increased in a [redacted]-year old with COVID-19 VACCINE ASTRAZENECA and reported the AE to AstraZeneca. Information regarding the origin of the vaccinee who experienced the event of Intracranial pressure increased is unknown. Vaccinee gender was reported in 475 of the reports with 319 (67%) occurring in females and 156 (33%) occurring in males. Vaccinee age was available in 401 of the reports and ranged from 20 to 97 years of age with a median of 54 years.

A total of 1449 AEs were reported within the 495 reports of booster dosing with COVID-19 VACCINE ASTRAZENECA through 04 January 2022. Of these 1449 AEs, 810 (56%) were reported as serious due to the AE being considered as medially important (682), the AE was reported to have resulted in disability (160), required hospitalization (107), was life threatening (32), and/or resulted in death (11). Cases may have met more than one criteria for seriousness.

A distribution of the AEs reported with a frequency ≥3 is provided in Table 26. The most frequently reported adverse events with COVID-19 VACCINE ASTRAZENECA booster were Headache, Pyrexia, Fatigue, Off-label use, and Nausea. Reports of off-label use mostly involved vaccinees receiving 3rd dose of COVID-19 VACCINE ASTRAZENECA in countries where use of the vaccine as a booster has or had not yet been authorized.

Outcome was reported for 1027 of the 1449 AEs reported, as follows: Not recovered (492, 48%), Recovered (285, 28%), Recovering (216, 21%), Recovered with sequelae (23, 2%), and Death (11, 1%).

Time to onset from vaccination to the event was available for 638 (44%) of the AEs reported, as follows: Within 1 day of vaccination (450, 71%), 2 – 5 days post-vaccination (80, 13%), 6 – 10 days post-vaccination (33, 5%), 11 – 30 days post-vaccination (39, 6%), and ≥31 days post-vaccination (36, 6%). Time to onset ranged from day of vaccination (0 days) to 274 days post-vaccination with a median time to onset of 1 day.

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Headache[a]	48	38	29	86
Pyrexia[a]	40	35	21	75
Fatigue[a]	28	39	4	67
Off-label use	45	1	11	46
Nausea[a]	15	25	10	40
Pain[a]	21	16	8	37
Pain in extremity[a]	21	15	2	36
Myalgia[a]	22	14	13	36
Chills[a]	18	15	4	33
Dizziness[a]	9	21	2	30
Arthralgia[a]	9	20	5	29

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Interchange of vaccine products	19	2	10	21
Asthenia[a]	10	10	6	20
Palpitations	4	16	3	20
Rash[a]	8	11	7	19
Diarrhoea[a]	6	13	4	19
Dyspnoea	4	15	3	19
Malaise[a]	8	9	2	17
Chest pain	1	16	1	17
Peripheral swelling	6	9	1	15
Vomiting[a]	5	9	3	14
Cough	7	7	3	14
COVID-19	4	9	3	13
Pruritus[a]	8	5	3	13
Lymphadenopathy[a]	5	8	0	13
Swelling[a]	7	5	0	12
Injection site pain[a]	7	4	4	11
Influenza	4	7	2	11
Paraesthesia[b]	6	5	4	11
Abdominal pain upper[a]	1	9	0	10
Tachycardia	1	9	2	10
Syncope	0	9	0	9

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Oropharyngeal pain	1	8	2	9
Abdominal pain[a]	4	4	3	8
Back pain[a]	4	4	3	8
Migraine[a]	2	5	0	8
Tremor[a]	1	6	0	7
Herpes zoster	2	5	1	7
Vaccination site pain[a]	6	1	6	7
Neck pain[a]	2	5	0	7
Muscle spasms	4	3	1	7
Illness[a]	2	5	0	7
Urticaria[a,b]	6	1	2	7
Influenza like illness[a]	3	4	0	7
Heavy menstrual bleeding	3	4	0	7
Hyperhidrosis	4	3	0	7
Lethargy[a]	4	2	0	6
Thrombocytopenia[a,b]	0	6	5	6
Blood pressure increased	5	1	5	6
Menstruation delayed	3	3	0	6
Tinnitus	2	4	2	6
Deep vein thrombosis[b]	0	6	0	6
Limb discomfort	3	3	0	6

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Anaphylactic reaction[a,b]	0	6	4	6
Hypersensitivity[b]	2	4	1	6
Hypoaesthesia[b]	2	4	1	6
Inappropriate schedule of product administration	6	0	5	6
Thrombosis	0	5	0	5
Musculoskeletal stiffness	2	3	2	5
Menstruation irregular	1	4	0	5
Chest discomfort	1	4	1	5
Night sweats[a]	1	4	0	5
Decreased appetite[a]	3	2	1	5
Vaginal haemorrhage	1	4	0	5
Epistaxis	1	4	1	5
Muscular weakness	2	3	0	5
Erythema[a]	3	2	1	5
Myocarditis[b]	0	5	1	5
Incorrect dose administered	4	1	5	5
Rash papular[a]	5	0	1	5
Insomnia	1	4	0	5
Lip swelling[a,b]	2	3	0	5
Menstrual disorder	3	2	0	5

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Rash erythematous[a]	2	2	1	4
Adverse event	4	0	3	4
Rhinorrhea	1	3	0	4
Expired product administered	4	0	3	4
Body temperature increased[a]	2	2	0	4
Feeling hot	1	3	0	4
Axillary pain[a]	2	2	0	4
Dysmenorrhea	3	1	0	4
Neuralgia[b]	2	2	1	4
Haemorrhage	2	2	1	4
Wrong product administered	4	0	4	4
Pain in jaw[a]	1	2	0	3
Tension headache[a]	2	1	0	3
Feeling cold[a]	2	1	1	3
Angioedema[a,b]	0	3	2	3
Nasopharyngitis	1	2	2	3
Heart rate increased	0	3	0	3
Peripheral coldness[a]	0	3	0	3
Anosmia[b]	1	2	1	3
Swelling face[a,b]	1	2	0	3
Hot flush	0	3	0	3

Table 26 Distribution of Adverse Events (n = 1449) with Frequency >3 with Booster Reporting Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Adverse Event Seriousness		Medically Confirmed Adverse Events	Total Adverse Events
	Non-Serious	Serious		
Extra dose administered	3	0	0	3
Hypertension	0	3	1	3
Blister	0	3	0	3
Amenorrhea	3	0	0	3
Paralysis	0	3	0	3
Intermenstrual bleeding	1	2	1	3
Polymenorrhoea	1	2	0	3
Dizziness postural	2	1	0	3
Somnolence[a]	2	1	1	3
Vision blurred	0	3	0	3
Tenderness	3	0	0	3
Epilepsy[b]	0	3	1	3
Contusion	1	2	0	3
Eye pain	1	2	1	3

[a] Labelled Adverse Drug Reaction (ADR) for COVID-19 VACCINE ASTRAZENECA as per AstraZeneca Company Core Data Sheet version 11.0.

[b] Current Adverse Event of Special Interest for COVID-19 VACCINE ASTRAZENECA

Fatal Reports

Cumulatively, there have been 4 reports involving 11 adverse events reporting a fatal outcome with a third booster dose of COVID-19 VACCINE ASTRAZENECA. These 4 reports with fatal outcome are summarized below:

- PPD : This spontaneous report involves a PPD -year-old PPD from PPD . Third booster dose of COVID-19 VACCINE ASTRAZENECA was administered on

an unknown date. The report stated that the vaccinee experienced death within hours after the 3rd dose of COVID-19 VACCINE ASTRAZENENCA. No further information regarding sequalae of events leading to fatal outcome, cause of death, medical history, or concomitant medications were provided for further case assessment.

- PPD : This spontaneous report involves a PPD-year-old PPD patient from the PPD. Third booster dose of COVID-19 VACCINE ASTRAZENECA was given on PPD after completed the primary vaccination series with COVID-19 VACCINE ASTRAZENECA. The vaccinee reportedly died of unknown causes 53 days later. No further information regarding sequalae of events leading to fatal outcome, cause of death medical history, or concomitant medications were provided for further case assessment.

- PPD : This spontaneous report involves a PPD-year-old PPD from PPD. Three months after second dose of COVID-19 VACCINE ASTRAZENECA and 1 day after booster with COVID-19 VACCINE (RECOMBINANT)-BIO-MANGUINHOS/ FIOCRUZ the vaccinee was reported to have experienced abdominal distension. On an unknown date, the patient died. No further information regarding sequalae of events leading to fatal outcome, cause of death, medical history, or concomitant medications were provided for further case assessment.

- PPD : This regulatory authority report involves a PPD-year-old PPD from the PPD. On an unknown date after receiving an unknown COVID-19 vaccine booster, the patient was reported to have experienced asthenia, feeling cold, fatigue, dyspnoea, chest pain, myocardial infarction and cardiac arrest. Seventeen (17) days after receiving booster, the patient reportedly experienced Cardiac death with fatal outcome. No autopsy was performed. The vaccinee did not have any known underlying cardiac conditions and influenza virus vaccine was the only concomitant medication reported. COVID-19 test performed on an unknown date was negative. No further information was provided. PPD provide plausible confounding factors for the myocardial infarction leading to fatal cardiac arrest.

Homologous/Heterologous Boosting Regimens

Of the 495 reports, 429 specified the regimens used for each of the 3 recommended vaccinations.

Homologous Dosing

Of the 429 reports specifying the vaccine regimens for all 3 vaccinations, 236 indicated homologous dosing where COVID-19 VACCINE ASTRAZENECA was used for all three vaccinations. A total of 674 adverse events were received within these 429 reports, of which 390 (58%) of the adverse events were considered serious and 147 (22%) of the adverse events were

medically confirmed. The distribution of the 674 adverse events contained within the 236 reports of homologous dosing with COVID-19 VACCINE ASTRAZENECA is provided in Table 27 below.

Table 27 Distribution of Adverse Events (n = 674) with Homologous Booster Dosing Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event **(Preferred Term)**	**Frequency of Events Reported**
Headache	40
Pyrexia	36
Fatigue	30
Nausea	22
Off-label use	20
Chills, Myalgia, Pain	16 each
Diarrhoea, Dizziness	13 each
Asthenia, Pain in extremity, Palpitations	12 each
Arthralgia	11 each
Malaise, Pruritus, Rash	10 each
Chest pain, Dyspnoea, Swelling	9 each
Abdominal pain	8
Paraesthesia, Vomiting	7 each
Cough, COVID-19, Heavy menstrual bleeding, Tachycardia	6 each
Anaphylactic reaction, Herpes zoster, Hypersensitivity, Hypoaesthesia, Illness, Lip swelling, Lymphadenopathy, Migraine, Muscle spasms, Tremor	5 each
Influenza, Injection site pain, Musculoskeletal stiffness, Oropharyngeal pain, Peripheral swelling, Syncope, Urticaria	4 each
Abdominal pain, Axillary pain, Blister, Body temperature increased, Decreased appetite, Deep vein thrombosis, Dysmenorrhoea, Epistaxis, Erythema, Expired product administered, Feeling hot, Hyperhidrosis, Inappropriate schedule of product administration, Lethargy, Lymph node pain, Menstruation delayed, Myocarditis, Neck pain, Neuralgia, Rhinorrhoea, Swelling face, Thrombosis, Vaginal haemorrhage	3 each
Adverse event, Albumin globulin ratio normal, Angioedema, Asthma, Cerebrovascular accident, Chest discomfort, Cluster headache, Contusion, Facial paralysis, Hot flush, Incorrect dose administered, Influenza like illness, Insomnia, Menstrual disorder, Night sweats, Pain in jaw, Paralysis, Pulmonary embolism, Sneezing, Thrombocytopenia, Tinnitus, Vaccination site pain	2 each
Abdominal discomfort, Ageusia, Anaphylactic shock, Anosmia, Arthritis, Back pain, Blindness unilateral, Blood glucose fluctuation, Blood pressure increased, Blood pressure measurement, Body temperature fluctuation, Bone pain, Breast	1 each

Table 27 Distribution of Adverse Events (n = 674) with Homologous Booster Dosing Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event **(Preferred Term)**	**Frequency of Events Reported**
cancer, Breast pain, Breast swelling, Cardiac asthma, Cardiac disorder, Cerebral haemorrhage, Coma, Condition aggravated, Contraindication to vaccination, COVID-19 pneumonia, Deafness, Deafness unilateral, Death, Depressed mood, Dermatitis acneiform, Dermatitis atopic, Disturbance in attention, Dizziness postural, Dyspepsia, Dysphonia, Ear pain, Erythema nodosum, Eye inflammation, Eye pain, Facial paresis, Fall, Feeling abnormal, Feeling cold, Gait disturbance, Goitre, Guillain-Barre syndrome, Haemorrhage, Heart rate decreased, Heart rate increased, Hemiplegia, Hormone level abnormal, Hospitalisation, Hypokinesia, Hypotension, Incontinence, Inflammation, Inflammatory bowel disease, Injection site mass, Intermenstrual bleeding, Intracranial pressure increased, Irritable bowel syndrome, Limb discomfort, Limb injury, Limb mass, Lip disorder, Lung neoplasm malignant, Lymphangiopathy, Medication error, Mental fatigue, Mitral valve incompetence, Mood swings, Mouth swelling, Muscular weakness, Nasopharyngitis, Nerve injury, Nervousness, Neuropathy peripheral, Nightmare, Ocular hyperaemia, Oesophageal pain, Oral herpes, Oxygen saturation abnormal, Panic attack, Papule, Paraesthesia oral, Peripheral coldness, Pharyngeal swelling, Photophobia, Pityriasis rosea, Pneumonia, Polymenorrhoea, Postprandial hypoglycaemia, Procedural dizziness, Psuedofolliculitis, Pulmonary pain, Pulmonary sepsis, Rash erythematous, Rash macular, Rash pruritic, Rectal haemorrhage, Respiratory rate increased, Scleritis, Seizure, Sepsis, Somnolence, Temperature intolerance, Throat tightness, Thyrotoxic crisis, Troponin increased, Vaccination complication, Vaginal discharge, Vertigo	

Fourteen (14) serious, medically confirmed reports involving homologous dosing with COVID-19 VACCINE ASTRAZENECA have been reported through 04 January 2022. Of these 14 serious, medically confirmed reports involving homologous dosing with COVID-19 VACCINE ASTRAZENECA all were reported from the United Kingdom. A total of 37 serious adverse events were included within these 14 serious, medically confirmed reports involving homologous dosing and included: Anaphylactic reaction (4), COVID-19 and Thrombocytopenia (2 each), Angioedema, Breast cancer, Chest discomfort, Chest pain, Deafness, Death, Dysphonia, Dyspnoea, Eye pain, Facial paralysis, Headache, Hypersensitivity, Injection site pain, Lung neoplasm malignant, Mitral valve incompetence, Muscle spasms, Myocarditis, Neuropathy peripheral, Paraesthesia, Photophobia, Pulmonary embolism, Pulmonary sepsis, Scleritis, Seizure, Sepsis, Tachycardia, Throat tightness, Tinnitus, and Troponin increased. Seriousness criteria for these 37 serious adverse events from medically confirmed reports with homologous booster included: AE resulted in death (1), AE was life threatening (10), AE resulted in hospitalization (9), AE resulted in disability (9), AE was considered medically important (24). A report may have contained more than one seriousness criteria. Outcome was available for 17 of

the 37 serious adverse events from medically confirmed reports with homologous booster as: Not recovered (10), Recovered (3), Recovering (2), Recovered with sequelae (1), and Death (1, AER 2021A812078).

There was no indication from any of the reports involving homologous booster dosing with COVID-19 VACCINE ASTRAZENECA that the AEs reported were different in nature or severity when compared to the known overall safety profile of COVID-19 VACCINE ASTRAZENECA.

Heterologous Boosting

Of the 429 reports specifying the vaccine regimens for all 3 vaccinations, 193 indicated heterologous booster dosing where COVID-19 VACCINE ASTRAZENECA was used as part of a vacation regimen with another COVID-19 vaccine. In most of these cases, it is difficult to determine at which point of the regimen COVID-19 VACCINE ASTRAZENECA was used (ie, as part of the initial vaccination or as booster). In 105 reports, information regarding which vaccine(s) were used as part of the heterologous dosing was not available. In the remaining 88 reports, 65 involved heterologous dosing with mRNA vaccines (20 with COVID-19 mRNA VACCINE BIONTECH/PFIZER, 45 with COVID-19 mRNA VACCINE MODERNA) and 23 involved heterologous booster dosing with COVID-19 VACCINE (RECOMBINANT)-BIO-MANGUINHOS/FIOCRUZ. A total of 542 adverse events were received within these 193 reports, of which 305 (56%) of the adverse events were considered serious and 88 (16%) of the adverse events were medically confirmed. The distribution of the 542 adverse events contained within the 193 reports of heterologous dosing with COVID-19 VACCINE ASTRAZENECA is provided in Table 28 below.

Table 28 Distribution of Adverse Events (n = 542) with Heterologous Booster Dosing Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Frequency of Events Reported
Headache	32
Fatigue	31
Pyrexia	28
Pain in extremity	22
Arthralgia, Interchange of vaccine products, Pain	14 each
Chills, Myalgia	13 each
Nausea, Off-label use	12 each
Dizziness	9
Cough	8

Table 28 Distribution of Adverse Events (n = 542) with Heterologous Booster Dosing Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Adverse Event (Preferred Term)	Frequency of Events Reported
Peripheral swelling	7
COVID-19, Dyspnoea, Palpitations, Vomiting	6 each
Back pain, Diarrhoea, Injection site pain, Malaise, Menstruation irregular, Syncope	5 each
Abdominal pain, Asthenia, Chest pain, Influenza like illness, Lymphadenopathy, Neck pain, Oropharyngeal pain, Rash, Rash popular, Tinnitus, Wrong product administered	4 each
Amenorrhoea, Haemorrhage, Hyperhidrosis, Inappropriate schedule of product administered, Influenza, Insomnia, Limb discomfort, Menstrual disorder, Menstruation delayed, Night sweats, Paraesthesia, Rash erythematous, Tension headache, Urticaria, Vision blurred	3 each
Abdominal distension, Abdominal pain upper, Aphonia, Cardiac flutter, chest discomfort, Decreased appetite, Deep vein thrombosis, Dizziness postural, Dysgeusia, Epistaxis, Hallucination, Heart rate irregular, Herpes zoster, Hypertension, Illness, Intermenstrual bleeding, Joint stiffness, Lethargy, Loss of consciousness, Maternal exposure during pregnancy, Migraine, Mouth ulceration, Muscle spasms, Oedema, Polymenorrhoea, Productive cough, Pruritus, Psoriasis, Somnolence, Swelling, Tachycardia, Tenderness, Thrombocytopenia, Vaginal haemorrhage	2 each
Accidental exposure to product, Adnexa uteri pain, Adverse event, Agitation, Allergy to vaccine, Alopecia, Anal haemorrhage, Anaphylactic reaction, Angioedema, Anosmia, Anxiety, Application site pain, Arthritis reactive, Atrial flutter, Axillary pain, Balance disorder, Blood pressure increased, Body temperature, Breast swelling, Cerebral venous thrombosis, Chronic fatigue syndrome, Confusional state, Conjunctivitis, Constipation, Contraindication to vaccination, Contusion, Diabetes mellitus, Discomfort, Drug ineffective, Drug intolerance, Dry skin, Dry throat, Dysmenorrhoea, Eczema, Epilepsy, Erythema, Eye swelling, Feeling abnormal, Feeling cold, Feeling hot, Flat affect, Flatulence, Flushing, Food intolerance, Freezing phenomenon, Genital herpes, Guillain-Barre syndrome, Hangover, Heart rate increased, Heavy menstrual bleeding, Hemiplegia, Hot flush, Hypersensitivity, Hypoaesthesia, Hypomenorrhoea, Hypotension, Immunisation, Injection related reaction, Leg amputation, Lymph gland infection, Lymphangiopathy, Mesenteric vein thrombosis, Muscle twitching, Musculoskeletal stiffness, Myocarditis, Neuralgia, Neuropathy peripheral, Ocular hyperaemia, Oral herpes, Oral pain, Osteoarthritis, Overdose, Oxygen saturation decreased, Pain in jaw, Paule, Paraesthesia oral, Peripheral coldness, Phantom limb syndrome, Pustular psoriasis, Rash pruritic, Respiratory distress, Rhinitis, Rhinorrhoea, Right ventricular failure, Scar, Sensitive skin, Sinus headache, Swelling of eyelid, Tetanus, Thermal burn, Thirst, Thrombosis, Tremor, Urine output, Vaccination site pain, Vertigo, Vertigo positional, Wheezing, Withdrawal syndrome	1 each

N Number

Eleven (11) serious, medically confirmed reports involving heterologous booster dosing with COVID-19 VACCINE ASTRAZENECA have been reported through 04 January 2022. Of these 11 reports, 4 originated from Brazil and the United Kingdom each and 1 each from [redacted] A total of 33 serious adverse events were included within these 11 serious, medically confirmed reports involving heterologous dosing and included: Headache (3), Arthralgia, Myalgia, Nausea, Pain, Pyrexia, Thrombocytopenia (2 each), and Abdominal distension, Angioedema, Cerebral venous thrombosis, Dizziness, Epilepsy, Erythema, Haemorrhage, Hemiplegia, Incorrect dose administered, Influenza, Injection site pain, Intermenstrual bleeding, Oxygen saturation decreased, Psoriasis, Pustular psoriasis, Rash, Tinnitus, and Vomiting (1 each). Seriousness criteria for these 33 serious adverse events from medically confirmed reports with heterologous booster included: AE considered medically important (22), AE resulted in disability (12), AE resulted in hospitalization (7), AE was considered life threatening (1), and AE resulted in death (1). A report may have contained more than one seriousness criteria.

Outcome was available for 26 of the 33 serious adverse events from medically confirmed reports with heterologous booster as: Recovered (12), Not recovered (7), Recovering (6), and Death (1, AER 2021A864972).

Upon review of these reports involving confirmed heterologous booster dosing with COVID-19 VACCINE ASTRAZENECA there was no indication that the nature or severity of these events were different from heterologous dosing when compared to homologous dosing with COVID-19 VACCINE ASTRAZENECA or the known overall safety profile of COVID-19 VACCINE ASTRAZENECA.

Unlisted Adverse Events Reported with Booster Dosing

Of the total of 1449 AEs reported with COVID-19 VACCINE ASTRAZENECA booster dosing through 04 January 2022, 663 from 353 reports were unlisted as per the Company Core Data Sheet (CDS) v11.0. Of these 663 unlisted adverse events with booster dosing, 137 (21%) were medically confirmed, 398 (60%) were serious, and 265 (40%) were non-serious. A summary of these unlisted adverse events by seriousness is provided in the following paragraphs.

Serious, Unlisted Adverse Events

A total of 398 serious, unlisted AEs were reported among the 663 total unlisted AEs involving booster dosing with COVID-19 VACCINE ASTRAZENECA through 04 January 2021. Of these 398 AEs, 309 (78%) were considered serious due to the AE being considered medically important, in 81 (20%) the AE was reported to have resulted in disability, in 74 (19%) the AE was reported to have required hospitalization, in 24 (6%) the reported AE was considered life

threatening and in 11 (3%) the AE was reported have have resulted in death. Cases may have met more than one criteria for seriousness.

Of these 398 serious, unlisted AEs, 51 were medically confirmed (from 20 unique reports) and 347 (from 157 unique reports) were not medically confirmed. In the report previously submitted to MHRA for the same review period, due to an Excel filtering error, it was incorrectly reported that a cumulative total of 19 (instead of 51) serious, medically confirmed unlisted adverse events involving booster COVID-19 VACCINE ASTRAZENECA were received 04 January 2022. AstraZeneca regrets and apologizes for this error.

A total of 183 reports involved confirmed homologous dosing in which a 2 dose regimen of COVID-19 VACCINE ASTRAZENECA was used followed by a third booster dose of COVID-19 VACCINE ASTRAZENECA. A distribution of the serious, unlisted AEs with reported frequency ≥3 with COVID-19 VACCINE ASTRAZENEA through 04 January 2022 by medical confirmation is included in below. The most frequently reported unlabeled, serious AEs were Chest pain, Palpitations, and Dyspnoea.

Outcome was reported for 280 of the 398 serious, unlisted AEs, as follows: Not recovered (157, 56%), Recovering (59, 21%), Recovered (41, 15%), Recovered with sequelae (12, 4%), and Death (11, 4%).

Time to onset from vaccination to the serious, unlisted event was available for 145 (36%) of the AEs reported, as follows: Within 1 day of vaccination (62, 43%), 2 – 5 days post-vaccination (35, 24%), 6 – 10 days post-vaccination (9, 6%), 11 – 30 days post-vaccination (22, 15%), and ≥31 days post-vaccination (17, 12%). Time to onset ranged from day of vaccination (0 days) to 246 days post-vaccination with a median time to onset of 2 days.

Table 29 Distribution of Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 398) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Serious, Unlisted Adverse Events			Time to Onset
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	Median, Range; (n)
Chest pain	16 (9)	1 (1)	15 (8)	2 days, <1 day – 6 days; (5)
Palpitations	16 (10)	0 (0)	16 (10)	2 days, <1 day – 4 days; (2)

Table 29 Distribution of Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 398) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Serious, Unlisted Adverse Events			Time to Onset Median, Range; (n)
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	
Dyspnoea	15 (7)	1 (1)	14 (6)	11 days, 4 days – 246 days; (3)
COVID-19	9 (4)	2 (2)	7 (2)	1 day, <1 day – 12 days; (3)
Peripheral swelling	9 (2)	0 (0)	9 (2)	1 day, <1 day – 18 days; (3)
Syncope	9 (4)	0 (0)	9 (4)	1 day, N/A (1)
Tachycardia	9 (1)	2 (1)	7 (0)	62 days, N/A (1)
Cough	7 (1)	0 (0)	7 (1)	2 days, <1 day – 4 days; (3)
Influenza	7 (3)	1 (0)	6 (3)	< 1 day, <1 day – 42 days; (5)
Deep vein thrombosis[a]	6 (3)	0 (0)	6 (3)	6.5 days, 5 days – 201 days; (4)
Oropharyngeal pain	6 (2)	0 (0)	6 (2)	1 day, <1 day – 2 days; (2)
Herpes zoster	5 (3)	0 (0)	5 (3)	4 days, 1 day – 30 days; (3)
Myocarditis[a]	5 (3)	1 (1)	4 (2)	<1 day, N/A (1)
Paraesthesia[a]	5 (2)	2 (1)	5 (1)	2 days, 1 day – 3 days; (2)
Thrombosis	5 (3)	0 (0)	5 (3)	6.5 days, 2 days – 36 days; (4)
Chest discomfort	4 (1)	1 (1)	3 (0)	3 days, 0 days – 6 days; (2)
Epistaxis	4 (3)	0 (0)	4 (3)	4 days, N/A; (1)
Heavy menstrual bleeding	4 (3)	0 (0)	4 (3)	20 days, N/A; (1)
Hypoaesthesia[a]	4 (3)	0 (0)	4 (3)	2 days, 1 day – 3 days; (3)

Table 29 Distribution of Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 398) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Serious, Unlisted Adverse Events			Time to Onset Median, Range; (n)
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	
Hypersensitivity[a]	4 (4)	1 (1)	3 (3)	<1 day, N/A; (2)
Insomnia	4 (2)	0 (0)	4 (2)	1 day, <1 day – 246 days; (3)
Menstruation irregular	4 (0)	0 (0)	4 (0)	40 days, N/A; (1)
Tinnitus	4 (2)	2 (1)	2 (1)	3.5 days, 1 day – 7 days; (4)
Vaginal haemorrhage	4 (2)	0 (0)	4 (2)	14 days, 1 day – 27 days; (2)
Blister	3 (3)	0 (0)	3 (3)	2 days, N/A; (1)
Epilepsy[a]	3 (0)	1 (0)	2 (0)	18 days, N/A; (1)
Feeling hot	3 (1)	0 (0)	3 (1)	N/A; (0)
Heart rate increased	3 (1)	0 (0)	3 (1)	N/A; (0)
Hot flush	3 (2)	0 (0)	3 (2)	<1 day, N/A; (1)
Hypertension	3 (1)	1 (0)	2 (1)	12 days, N/A; (1)
Limb discomfort	3 (1)	0 (0)	3 (1)	1 day, N/A; (1)
Menstruation delayed	3 (1)	0 (0)	3 (1)	N/A; (0)
Muscle spasms	3 (2)	1 (1)	2 (1)	N/A; (0)
Muscular weakness	3 (0)	0 (0)	3 (0)	10.5 days, <1 day – 21 days; (2)
Paralysis	3 (2)	0 (0)	3 (2)	3 days, N/A; (1)
Rhinorrhoea	3 (2)	0 (0)	3 (2)	<1 day, N/A; (1)
Vision blurred	3 (0)	0 (0)	3 (0)	214 days, 182 days – 246 days; (2)

[a] Current Adverse Event of Special Interest for COVID-19 VACCINE ASTRAZENECA.

Of all 398 serious, unlisted AEs a total of 63 AEs from 47 unique reports are considered Adverse Events of Special Interest (AESIs) for COVID-19 VACCINE ASTRAZENECA and are being

closely monitored as part of AstraZeneca's ongoing surveillance activities. A summary table with information for these serious, unlisted AESIs is provided in Table 30.

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
Deep vein thrombosis	6 (0)	PPD PPD	Homologous	8 days	AE resulted in hospitalisation	Recovering
		PPD PPD	Homologous	Unknown	AE considered life-threatening; AE resulted in hospitalisation; AE resulted in disability	Not recovered
			Homologous	201 days	AE considered life-threatening; AE resulted in hospitalisation; AE resulted in disability	Recovering
		PPD	Heterologous	5 days	AE considered life-threatening	Not recovered
		PPD	Unknown	Unknown	AE considered medically important	Not recovered

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD				
		PPD	Heterologous	5 days	AE considered life threatening	Not recovered
Myocarditis	5 (1)	PPD	Homologous	Unknown	AE considered medically important	Not recovered
		PPD	Homologous	<1 day	AE resulted in hospitalisation; AE considered medically important	Recovered with sequelae
		PPD	Unknown	Unknown	AE resulted in hospitalisation; AE considered medically important	Not recovered
		PPD	Homologous	Unknown	AE considered medically important	Unknown

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD	Heterologous	Unknown	AE resulted in hospitalisation	Not recovered
Paraesthesia	5 (2)	PPD	Unknown	Unknown	AE resulted in hospitalisation	Unknown
		PPD	Heterologous	1 day	AE considered medically important	Not recovered
		PPD	Homologous	Unknown	AE considered medically important	Unknown
		PPD	Homologous	3 days	AE considered medically important	Not recovered
		PPD	Heterologous	Unknown	AE considered medically important	Recovering
Hypersensitivity	4 (1)	PPD	Homologous	Unknown	AE considered medically important	Recovering

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD	Homologous	Unknown	AE resulted in hospitalisation; AE considered medically important	Recovering
		PPD	Homologous	<1 day	AE considered medically important	Recovering
		PPD	Homologous	<1 day	AE considered medically important	Recovering
Hypoaesthesia	4 (0)	PPD	Homologous	1 day	AE considered medically important	Recovered
		PPD	Homologous	2 days	AE considered medically important	Not recovered
		PPD	Homologous	3 days	AE considered medically important	Not recovered
		PPD	Heterologous	Unknown	AE considered medically important	Recovering

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
PPD	3 (1)	PPD (Unknown/PPD	Unknown	Unknown	AE considered medically important	Recovering
		PPD	Heterologous	18 days	AE resulted in disability	Unknown
		PPD	Unknown	Unknown	AE resulted in hospitalisation; AE resulted in disability; AE considered medically important	Recovering
Anosmia	2 (1)	PPD	Unknown	Unknown	AE resulted in hospitalisation; AE considered medically important	Unknown
		PPD	Heterologous	Unknown	AE considered medically important	Unknown

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
Cerebrovascular accident	2 (0)	PPD	Homologous	80 days	AE considered life threatening	Not recovered
		PPD	Homologous	91 days	AE resulted in disability; AE considered medically important	Not recovered
PPD	2 (0)	PPD	Heterologous	12 days	AE resulted in hospitalisation; AE considered medically important	Unknown
		PPD	Homologous	22 days	AE considered live-threatening; AE resulted in hospitalisation	Not recovered
Hypotension	2 (0)	PPD	Homologous	1 day	AE considered medically important	Recovered
		PPD	Heterologous	Unknown	AE considered medically important	Recovered

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
Neuralgia	2 (0)	PPD (Unknown/Unknown/PPD)	Homologous	<1 day	AE considered medically important	Not recovered
		PPD	Homologous	Unknown	AE resulted in disability; AE considered medically important	Recovering
Neuralgia	2 (0)	PPD	Heterologous	Unknown	AE considered medically important	Not recovered
		PPD	Homologous	Unknown	AE considered life-threatening; AE resulted in disability; AE considered medically important	Unknown
Neuropathy peripheral	2 (1)	PPD	Heterologous	Unknown	AE considered medically important	Not recovered

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD	Homologous	Unknown	AE considered life-threatening; AE resulted in disability; AE considered medically important	Unknown
Pulmonary embolism	2 (1)	PPD	Homologous	Unknown	AE considered life threatening	Unknown
		PPD	Homologous	228 days	AE considered life threatening; AE resulted in hospitalisation; AE resulted in disability	Not recovered
Seizure	2 (1)	PPD	Unknown	Unknown	AE considered medically important	Recovering
		PPD	Homologous	11 days	AE considered life-threatening; AE resulted in disability;	Not recovered

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
					AE considered medically important	
Troponin increased	2 (1)	PPD	Homologous	Unknown	AE resulted in hospitalisation; AE considered medically important	Unknown
		PPD	Unknown	Unknown	AE resulted in hospitalisation; AE considered medically important	Unknown
Ageusia	1 (1)	PPD	Unknown	Unknown	AE resulted in hospitalisation	Unknown
Bell's palsy	1 (0)	PPD	Unknown	9 days	AE considered medically important	Recovering
Cardiac asthma	1 (0)	PPD	Homologous	<1 day	AE considered medically important	Not recovered
Cerebral venous thrombosis	1 (1)	PPD	Heterologous	18 days	AE resulted in disability	Unknown

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD PPD				
Cerebral venous thrombosis	1 (1)	PPD	Heterologous	18 days	AE resulted in disability	Unknown
Chronic fatigue syndrome	1 (0)	PPD	Heterologous	Unknown	AE considered medically important	Not recovered
Conjunctivitis	1 (0)	PPD	Heterologous	1 day	AE considered medically important	Recovering
COVID-19 pneumonia	1 (0)	PPD	Homologous	Unknown	AE resulted in hospitalisation	Recovering
Encephalitis	1 (0)	PPD	Unknown	Unknown	AE considered medically important	Unknown
PPD	1 (1)	PPD	Homologous	Unknown	AE considered life-threatening; AE resulted in disability;	Unknown

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
					AE considered medically important	
PPD	1 (0)	PPD	Homologous	<1 day	AE considered medically important	Not recovered
PPD	1 (0)	PPD	Unknown	Unknown	AE resulted in hospitalization; AE considered medically important	Not recovered
Mechanical ventilation	1 (0)	PPD	Unknown	Unknown	AE resulted in disability	Unknown
Mesenteric vein thrombosis	1 (0)	PPD	Heterologous	1 day	AE resulted in hospitalisation; AE considered medically important	Not recovered
Myocardial infarction	1 (0)	PPD	Unknown	Unknown	AE resulted in death	Died
PPD	1 (0)	PPD	Unknown	Unknown	AE resulted in disability;	Not recovered

Table 30 Summary Tabulation of Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 64)

Reported Serious, Unlisted Adverse Event	Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	Reported AESI Seriousness Criteria	Reported AE Outcome
	Total number of Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age/Gender/Country of Origin)	Booster Dosing Regimen			
		PPD			AE considered medically important	
Pericarditis	1 (0)	PPD	Unknown	Unknown	AE resulted in hospitalisation; AE considered medically important	Not recovered
Pneumonia	1 (0)	PPD	Homologous	11 days	AE resulted in hospitalisation; AE resulted in disability	Not recovered
Right ventricular failure	1 (0)	PPD	Heterologous	Unknown	AE resulted in disability	Not recovered

AE Adverse Event, AESI Adverse Events of Special Interest, UK United Kingdom, Unk Unknown, yrs Years..

Non-Serious, Unlisted Adverse Events Reported with Booster Dosing

A total of 265 non-serious, unlisted AEs were reported among the 663 total unlisted AEs involving booster dosing with COVID-19 VACCINE ASTRAZENECA through 04 January 2021.

Of these 265 non-serious, unlisted AEs, 86 were medically confirmed (from 62 unique reports) and 179 (from 121 unique reports) were not medically confirmed. A total of 105 reports involved confirmed homologous dosing in which a 2 dose regimen of COVID-19 VACCINE ASTRAZENECA was used followed by a third booster dose of COVID-19 VACCINE ASTRAZENECA. A distribution of the non-serious, unlisted AEs with reported frequency ≥3 with COVID-19 VACCINE ASTRAZENEA through 04 January 2022 by medical confirmation is included in Table 31 below. The most frequently reported unlabelled, non-serious AEs were Off-label use, Interchange of vaccine products, and Cough.

Outcome was reported for 144 of the 265 non-serious, unlisted AEs, as follows: Not recovered (74, 51%), Recovered (43, 30%), Recovering (26, 18%), and Recovered with sequelae (1, <1%).

Time to onset from vaccination to the non-serious, unlisted event was available for 106 (74%) of the AEs reported, as follows: Within 1 day of vaccination (77, 73%), 2 – 5 days post-vaccination (12, 11%), 6 – 10 days post-vaccination (3, 3%), 11 – 30 days post-vaccination (7, 7%), and ≥31 days post-vaccination (7, 7%). Time to onset ranged from day of vaccination (0 days) to 164 days post-vaccination with a median time to onset of 1 days.

Table 31 Distribution of Non-Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 265) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Non-Serious, Unlisted Adverse Events			Time to Onset Median, Range; (n)
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	
Off-label use	45 (20)	11 (3)	34 (17)	<1 days, <1 day; (6)
Interchange of vaccine products	19 (0)	10 (0)	9 (0)	0.5 days, <1 day – 1 day; (2)
Cough	7 (5)	3 (2)	4 (3)	1 day, <1 day – 1 day; (4)
Paraesthesia[a]	6 (5)	2 (2)	4 (3)	1 day, 1 day – 12 days; (3)

Table 31 Distribution of Non-Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 265) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Non-Serious, Unlisted Adverse Events			Time to Onset Median, Range; (n)
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	
Peripheral swelling	6 (2)	1 (0)	5 (2)	1 day, <1 day – 164 days; (6)
Inappropriate schedule of product administrated	6 (3)	5 (2)	1 (2)	<1 day, N/A; (1)
Blood pressure increased	5 (1)	5 (1)	0 (0)	<1 day, <1 day; (5)
Wrong product administered	4 (0)	4 (0)	0 (0)	< 1 day, <1 day; (3)
Adverse event	4 (2)	3 (1)	1 (1)	N/A; (0)
Musculoskeletal stiffness	4 (3)	2 (2)	2 (1)	N/A; (0)
Incorrect dose administered	4 (2)	1 (2)	3 (0)	<1 day, <1 day; (4)
Palpitations	4 (2)	3 (2)	1 (0)	1 day, <1 day – 1 day; (3)
COVID-19	4 (2)	1 (1)	3 (1)	34.5 days, 13 days – 56 days; (2)
Dyspnoea	4 (2)	2 (0)	2 (2)	8 days, < 1 day – 16 days; (2)
Expired product administered	4 (3)	3 (3)	1 (0)	<1 day, <1 day – 17 days; (3)
Muscle spasms	4 (3)	0 (0)	4 (3)	N/A; (0)
Influenza	4 (1)	1 (0)	3 (1)	1 day, <1 day – 1 day; (4)
Oropharyngeal pain	3 (2)	2 (2)	1 (0)	1 day; 1 day – 2 days; (3)
Menstrual disorder	3 (1)	0 (0)	3 (1)	4 days; <1 day – 11 days; (3)
Heavy menstrual bleeding	3 (3)	0 (0)	3 (3)	23 days; 19 – 27 days; (2)
Dysmenorrhoea	3 (2)	0 (0)	3 (2)	81 days, N/A; (1)

Table 31 Distribution of Non-Serious, Unlisted Adverse Events as per Company Core Data Sheet v11.0 (n = 265) Reported with Frequency >3 in Booster Reports Involving COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022

Reported Serious, Unlisted Adverse Event (Preferred Term)	Non-Serious, Unlisted Adverse Events			Time to Onset Median, Range; (n)
	Total (reports involving homologous dosing)	Medically Confirmed (reports involving homologous dosing)	Non-Medically Confirmed (reports involving homologous dosing)	
Menstruation delayed	3 (2)	0 (0)	3 (2)	61 days, N/A; (1)
Amenorrhoea	3 (0)	0 (0)	3 (0)	3.5 days, 0 days – 7 days; (2)
Tenderness	3 (0)	0 (0)	3 (0)	0.5 days, <1 day – 1 day; (2)
Extra dose administered	3 (0)	0 (0)	3 (0)	N/A; (0)
Limb discomfort	3 (0)	0 (0)	3 (0)	1 day, N/A; (1)

[a] Current Adverse Event of Special Interest for COVID-19 VACCINE ASTRAZENECA

Of all 265 non-serious, unlisted AEs a total of 15 AEs from 13 unique reports are considered Adverse Events of Special Interest (AESIs) for COVID-19 VACCINE ASTRAZENECA and are being closely monitored as part of AstraZeneca's ongoing surveillance activities. A summary table with information for these non-serious, unlisted AESIs is provided in Table 32.

Table 32 Summary Tabulation of Non-Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 15)

Reported Non-Serious, Unlisted Adverse Event	Non-Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	AE Outcome
	Total number of Non-Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age / Gender / Country of Origin)	Booster Dosing Regimen		
Paraesthesia	6 (2)	PPD [redacted]	Homologous	1 day	Not recovered
		PPD [redacted]	Homologous	12 days	Unknown
		PPD [redacted]	Homologous	Unknown	Unknown
		PPD [redacted]	Homologous	Unknown	Not recovered
		PPD [redacted]	Homologous	1 day	Recovered

Table 32 Summary Tabulation of Non-Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 15)

Reported Non-Serious, Unlisted Adverse Event	Non-Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	AE Outcome
	Total number of Non-Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age / Gender / Country of Origin)	Booster Dosing Regimen		
		PPD	Homologous	Unknown	Unknown
Hypersensitivity	2 (0)	PPD	Homologous	Unknown	Unknown
		PPD	Heterologous	Unknown	Recovering
Hypoaesthesia	2 (1)	PPD	Homologous	< 1 day	Recovered
		PPD	Homologous	Unknown	Unknown

Table 32 Summary Tabulation of Non-Serious, Unlisted (as per Company Core Data Sheet v11.0) Adverse Events of Special Interest (AESI) Reported with COVID-19 VACCINE ASTRAZENECA (Suspect or Co-Suspect) through 04 January 2022 (n = 15)

Reported Non-Serious, Unlisted Adverse Event	Non-Serious, Unlisted Adverse Events			Time from Booster dose to AE Onset	AE Outcome
	Total number of Non-Serious, Unlisted AESIs Reported (number medically confirmed)	Adverse Event Number (Vaccinee age / Gender / Country of Origin)	Booster Dosing Regimen		
Neuralgia	2 (1)	PPD	Homologous	1 day	Recovering
		PPD	Heterologous	124 days	Not recovered
Ageusia	1 (0)	PPD	Homologous	1 day	Not recovered
Anosmia	1 (0)	PPD	Homologous	1 day	Not recovered
PPD	1 (0)	PPD	Homologous	<1 day	Recovered

AE Adverse Events, AESI Adverse Events of Special Interest, UK United Kingdom, Unk Unknown, Yrs Years.

Summary

Based upon this cumulative review of booster reports involving COVID-19 VACCINE ASTRAZENECA through 04 January 2022, no new safety concerns were identified. Most of the reported adverse events with COVID-19 VACCINE ASTRAZENECA are listed in the Company Core Data Sheet (v11.0) and/or are Adverse Events of Special Interest (AESI) for the product and are under close monitoring by AstraZeneca. As has been a consistent pattern for COVID-19 VACCINE ASTRAZENECA overall, analysis shows a higher number of serious adverse events compared to non-serious adverse events with booster dosing. For Regulatory Authority reports received in the UK, which is the majority of reports received for COVID-19 VACCINE ASTRAZENECA as a booster, in the absence of medical confirmation, the seriousness assessment provided by the initial reporter is used as the source data. Thus, the high number of serious reports may indicate a different understanding of seriousness definitions for those events reported by non-medically trained individuals.

A review of booster reports involving homologous and heterologous dosing with COVID-19 VACCINE ASTRAZENECA within the vaccination regimen did not identify any new safety concerns. The nature and severity of adverse events reported with homologous or heterologous dosing did not differ from the currently known safety profile of COVID-19 VACCINE ASTRAZENECA.

Conclusion

No new safety concern has been identified for COVID-19 VACCINE ASTRAZENECA as part of a booster regimen and no changes to the labelling or the RMP are required. AstraZeneca will continue to monitor adverse event reports involving booster dosing with COVID-19 VACCINE ASTRAZENECA as part of ongoing routine surveillance activities.

15.2.6 Capillary leak syndrome

Request

AstraZeneca received the following requests from PRAC in the Assessment Report (AR) for the 7th and 8th SSRs (review periods: 01 August 2021 – 30 September 2021 and 01 October 2021 – 30 November 2021 respectively):

"*Capillary Leak Syndrome: The MAH is requested to propose an updated strategy to identify cases of CLS. This include a revision of the list of search terms that was proposed by PRAC at the time of the assessment of signal EPIT 19672. In addition, a suitable TTO should be defined (for example ≤ 5 days) for case analysis. The MAH should continue to explore new information on potential mechanisms leading to CLS and discuss how this information applies to Vaxzevria."*

"Capillary Leak Syndrome: The MAH should discuss new cases from spontaneous reporting and the literature; in addition, the MAH should search the literature for new information on possible mechanisms."

AstraZeneca's response to these requests is provided below.

Review of cases

A cumulative search 29 December 2020 – 28 December 2021 and a search of the reporting period 29 June 2021 – 28 December 2021 of the AstraZeneca Global Patient Safety Database was conducted on 29 December 2021 for adverse event reports of Capillary leak syndrome (CLS) in association with the use of AZD1222.

An updated strategy to identify cases of CLS included using the list of search terms that was proposed by PRAC at the time of the assessment of signal EPIT 19672. Definitive cases and 'probable' cases of CLS were derived from this search strategy and dataset using the medical definition for CLS. The medical definition used to identify CLS was 'Idiopathic systemic capillary leak syndrome (ISCLS) is a rare disorder characterized by episodes of severe hypotension, hypoalbuminemia, and haemoconcentration Aneja et al 2021.' The criteria for determining case definition for CLS was standardized by the company.

The search strategy included PTs under the MedDRA (version 24.1): Capillary leak syndrome; Capillary permeability increased; Generalised oedema; Blood albumin abnormal; Blood albumin decreased; Hypoalbuminaemia; Hypoproteinaemia; Haematocrit increased; Haemoconcentration; Hypovolaemia; Hypovolaemic shock; Protein total decreased, and Volume blood decreased.

<u>Cumulative review through 28 December 2021</u>

Cumulatively, the above search strategy identified 178 cases of CLS (172 spontaneous, 5 literature and 1 non-interventional study), reporting 184 AEs as follows: Capillary leak syndrome (44), Capillary permeability increased (2), Generalised oedema (35), Blood albumin abnormal (1), Blood albumin decreased (3), Haematocrit increased (14), Hypovolaemia (8), Hypoalbuminaemia (3) and Hypovolaemic shock (74). Of the 178 cases, 147 (83%) cases were reported as serious due to the AE being considered as medically important event (107), the AE was reported to have resulted in disability (7), AE was reported to have required hospitalization (34), AE was considered life threatening (20), or the AE was reported as resulting in death (10). The remaining 31(17%) cases were reported non-serious. Out of 178 cases, 56 (32%) were medically confirmed and 122 (69%) were consumer reports.

Of the 178 cases, there were 112 (63%) concerning females, 55 (31%) males and 11 (6%) cases of unknown gender. Amongst the 178 cases, 1 case occurred in a 20 year old patient,

and the age range was 21 to 40 years in 34 (19%) cases, 41 to 65 years in 93 (52%) cases, in 26 (15%) cases the age group was elderly (>65 years) and for the remaining 24 (14%) cases the age was not provided.

Time-to-onset (TTO) was reported for 136 (76%) cases and was unknown for 42 (24%). In 161 cases events were reported after the first dose, in 6 cases events were reported after the second dose and for 11 cases dose information was unknown (Table 33).

Table 33 TTO for CLS Cases Cumulative Period through 28 December 2021 (From First Dose/Second Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
00 Under 1 day	62	2		36.0
01 day	21			11.8
02 days	5	1		3.4
03 days	6			3.4
04 days	3			1.7
05 days	2			1.1
06 days	3			1.7
07 days	2			1.1
08 days	1			0.6
09 days	2			1.1
10 to 20 days	10	1		6.2
21 to 30 days	3			1.7
31 to 40 days	5			2.8
41 to 50 days	1			0.6
51 to 60 days	0			0.0
61 days and above	6			3.4
Unknown days (missing)	29	2	11	23.6

TTO Time To Onset.

For the 178 cases, the event outcomes were reported as follows: 10 (6%) with fatal outcome, 33 (19%) were not recovered, 42 (24%) were recovered, 1(<1%) was recovered with sequelae, 21(12%) were recovering and 71 (40%) events were with unknown outcome.

Definitive/probable CLS cases – Cumulative period

Having obtained the dataset using the above search strategy, cases were classified as definitive or probable cases of CLS using the medical definition for CLS (Appendix 18).

The evaluation identified 46 (26%) definitive or probable cases of CLS, reporting 46 AEs as follows: Capillary leak syndrome (44) and Capillary permeability increased (2).

Of the 46 cases, 39 (85%) cases were considered serious due to the AE being considered a medically important event (24), the AE was reported to have resulted in disability (3), the AE was reported to have required hospitalization (13), AE was reported as life threatening (3), or the AE was reported to have resulted in death (5). The remaining 7 (15%) cases were non-serious. Out of 46 cases, 21 (46%) were medically confirmed and 25 (54%) were consumer reports.

There were 25 (54%) cases for females, 13 (28%) for males and 8 (17%) of unknown gender. Amongst 46 cases, 1 case belongs to a PPD year old patient, the age range was 41 to 65 years in 19 (41%) cases, in 15 (32%) cases the age group was elderly (>65 years) and for the remaining 11 (24%) cases the age was not provided.

Time-to-onset (TTO) was reported for 24 cases and was unknown for 22. In 40 cases events were reported after the first dose, in 2 cases events were reported after the second dose and for 4 cases dose information were unknown (Table 34).

Table 34 TTO for CLS Cases Cumulative Period through 28 December 2021 (From First Dose/Second Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
00 Under 1 day	3			6.5
01 day	2			4.3
02 days	4			8.7
03 days	2			4.3
04 days	2	1		6.5
05 days	1			2.2
06 days	1			2.2
07 days	0			0.0
08 days	1			2.2
09 days	1			2.2
10 to 20 days	1			2.2
21 to 30 days	1			2.2
31 to 40 days	2			4.3
41 to 50 days	0			0.0

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
51 to 60 days	0			0.0
61 days and above	2			4.3
Unknown days (missing)	17	1	4	47.8

CLS Capillary Leak Syndrome, TTO Time to Onset.

For the 46 cases, the event outcomes were as follows: 5 (11%) with fatal outcome, 10 (22%) were not recovered, 7 (15%) were recovered, 1 (2%) was recovered with sequelae, 9 (20%) were recovering and 14 (30%) events were with unknown outcome.

Amongst 46 cases, 5 were with fatal outcome. The case details were described below.

- PPD : PPD -year-old PPD reported to have experienced capillary leak syndrome on day 1 after 1st dose of COVID-19 VACCINE ASTRAZENECA and was reported to have died due to capillary leak syndrome, blood albumin decreased, capillary nail refill test abnormal, myocardial depression, haematocrit increased, pyrexia, myalgia, ejection fraction decreased, vasoplegia syndrome, hypotension, hypovolaemia and presyncope after 81 hours (3 days). The relevant medical history included hypergammaglobulinaemia benign monoclonal, PPD and capillary leak syndrome. Limited information on etiologic and diagnostic work up as well on autopsy details.
- PPD : PPD -year-old PPD was reported to have experienced capillary leak syndrome on day 2 after 1st dose of COVID-19 VACCINE ASTRAZENECA and reportedly died due to capillary leak syndrome, fatigue, multiple organ dysfunction syndrome, myalgia, polycythaemia, syncope and thrombocytopenia on an unknown date. There was no relevant medical history and concomitant medication reported in this case and information was limited (autopsy performed unknown).
- PPD : PPD -year-old PPD was reported to have experienced capillary leak syndrome on day 4 after 1st dose of COVID-19 VACCINE ASTRAZENECA and was reported to have died due to capillary leak syndrome, hypotension, dyspnoea and taste disorder on day 50. The relevant medical history included cardiac insufficiency and heart failure. Limited information on etiologic and diagnostic work up as well on autopsy details.
- PPD : Patient with unknown demographics was reported to have died due to systemic capillary leak syndrome on an unknown date post 1st dose of COVID-19 VACCINE ASTRAZENECA. There was no relevant medical history, start date of event and concomitant medication reported in this case and information was limited (autopsy performed unknown).
- PPD : Patient with unknown demographics was reported to have died due to capillary leak syndrome, PPD and thrombosis with thrombocytopenia syndrome) on an unknown date post 1st dose of COVID-19 VACCINE ASTRAZENECA. There was no relevant medical history, start date of event and concomitant medication reported in this case and information was limited (autopsy performed unknown).

There were three (3) fatal cases (PPD) assessed by AstraZeneca as WHO-UMC Possible causality assessment within TTO: 0-7 days, however lack of information such as relevant medical history, concomitant medication, etiologic and diagnostic work up as well as on autopsy details precludes a comprehensive causal assessment. Two (2) fatal cases with TTO unknown were assessed by AstraZeneca as WHO-UMC Unassessable-Unclassifiable. These 2 cases also contained limited information on confounders/risk factors.

Among all 46 cases, there were cases that reported relevant risk factors for CLS in the reported medical history, including: prior CLS (4), COVID-19 (1), diabetes mellitus (3), hypergammaglobulinaemia benign monoclonal (2), immunodeficiency/infection/surgery (4), systemic inflammatory response syndrome (1), cardiac insufficiency (1), hypovolemia (1), acute myocardial infarction (1), cardiogenic shock (1), cardiac arrest (1), cardiac failure (1) and multiple sclerosis (1). Most of the cases had limited information with respect to medical history and concomitant medication (28 cases).

AstraZeneca also assessed WHO-UMC causality for the 46 cases of CLS using a risk window of 0 – 7 days. a risk window consideration of 0-7 days for all 47 cases. Amongst 46 cases, 16 cases were identified within the TTO of 0-7 days and WHO-UMC causality was considered as possible. However, 8 of 16 cases were noted with risk factors as follows: CLS (2), diabetes mellitus (1), hypergammaglobulinaemia benign monoclonal (2), systemic inflammatory response syndrome (1), acute myocardial infarction (1), cardiac insufficiency (1), cardiogenic shock (1), cardiac arrest (1), hypovolemia (1), cardiac failure (1) and multiple sclerosis (1). In the remaining 8 cases, the information was limited on the medical history, concomitant medications and etiologic and diagnostic work up.

Amongst 46 cases, 8 (17%) cases were outside the risk window of 0-7 days, of these 8 cases, 7 had limited information on medical history, concomitant medications and etiologic and diagnostic work up and 1 had confounding medical history of diabetes, hence WHO-UMC causality was considered as unlikely for these cases.

Amongst 46 cases, for 22 cases the TTO was unknown hence WHO-UMC was considered as unassessable/unclassifiable. However, 5 cases were noted with risk factors as follows: CLS (2), diabetes (1), COVID-19 (1), immunodeficiency/infection/surgery (2). In the remaining 17 cases the information was limited on the medical history, concomitant medications and etiologic and diagnostic work up.

Interval review (29 June 2021 – 28 December 2021)

The new cases within the interval period for this PBRER are discussed below. It is noted that since the last summary safety report, which data-locked on 30 November 2021, there were 13 new cases of CLS reported.

For the interval period of the PBRER, the above search strategy identified 127 case reports of CLS (122 spontaneous, 5 literature), reporting 131 AEs as follows: Capillary leak syndrome (27), Capillary permeability increased (1), Generalised oedema (19), Blood albumin abnormal (1), Blood albumin decreased (2), Haematocrit increased (7), Hypovolaemia (7) and Hypovolaemic shock (67).

Of the 127 cases, 112 (88%) cases were reported as serious due to the AE being considered as medically important event (88), the AE was reported to have resulted in disability (3), required hospitalization (23), was reported as life threatening (13), and/or was reported to have resulted in death (8). The remaining 15 (12%) cases were non-serious. Out of 127 cases, 33 (26%) were medically confirmed and 94 (74%) were consumer reports.

There were 73 (58%) females, 47 (37%) males and 7 (6%) of unknown gender. Amongst 127 cases, 1 case belongs to a 20 year old patient, the age range was 21 to 40 years in 27 (21%) cases, 41 to 65 years in 68 (54%) cases, in 19 (15%) cases the age group was elderly (>65 years) and for the remaining 12 (9%) cases the age was not provided.

Time-to-onset (TTO) was reported for 101 cases and was unknown for 26. In 115 cases events were reported after the first dose, in 4 cases events were reported after the second dose and for 8 cases dose information were unknown (Table 35).

Table 35 TTO for CLS Cases - Interval Period: 29 June 2021 – 28 December 2021 (From First Dose/Second Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
00 Under 1 day	55	1		44.1
01 day	15			11.8
02 days	2			1.6
03 days	3			2.4
04 days	2			1.6
05 days	1			0.8
06 days	1			0.8
07 days	1			0.8
08 days	1			0.8
09 days	2			1.6
10 to 20 days	6	1		5.5
21 to 30 days	1			0.8
31 to 40 days	3			2.4
41 to 50 days	0			0.0
51 to 60 days	0			0.0
61 days and above	6			4.7
Unknown days (missing)	16	2	8	20.5

CLS Capillary Leak Syndrome, TTO Time to Onset.

For the 127 cases, the event outcomes were as follows: 8 (6%) with fatal outcome, 20 (16%) were not recovered, 31 (24%) were recovered, 1 (1%) was recovered with sequelae, 11 (9%) were recovering and 56 (44%) events were with unknown outcome.

Definitive/probable CLS cases – Reporting interval (29 June 2021 – 28 December 2021)

Having obtained the dataset using the above search strategy, definitive and probable cases were then determined using the medical definition for CLS (Appendix 18).

From this, there were identified 28 cases of CLS, reporting 28 AEs as follows: Capillary leak syndrome (27) and Capillary permeability increased (1).

Of the 28 cases, 24 (86%) cases were reported as serious due to the AE being considered as medically important event (13), the AE reportedly resulted in disability (2), required hospitalization (10), was reported as life threatening (3), and/or reportedly resulted in death (4). The remaining 4 (14%) cases were non-serious. Out of 28 cases, 12 (43%) were medically confirmed and 16 (57%) were consumer reports.

There were 12 (43%) cases for females, 10 (36%) for males and 6 (21%) of unknown gender. Amongst 28 cases, 1 case occurred in a [redacted] year old patient, the age range was 41 to 65 years in 11 (39%) cases, in 11 (39%) cases the age group was elderly (>65 years) and for the remaining 5 (18%) cases the age was not provided.

Time-to-onset (TTO) was reported for 14 (50%) cases and was unknown for the remaining 14. In 24 cases events were reported after the first dose, in 1 case event was reported after the second dose and for 3 cases dose information were unknown (Table 36).

Table 36 TTO for CLS Cases - Interval Period: 29 June 2021 – 28 December 2021 (From First Dose/Second Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
00 Under 1 day	1			3.6
01 day	2			7.1
02 days	1			3.6
03 days	2			7.1
04 days	1			3.6
05 days	0			0.0
06 days	1			3.6
07 days	0			0.0

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (Dose Unknown)	%
08 days	1			3.6
09 days	1			3.6
10 to 20 days	1			3.6
21 to 30 days	0			0.0
31 to 40 days	1			3.6
41 to 50 days	0			0.0
51 to 60 days	0			0.0
61 days and above	2			7.1
Unknown days (missing)	10	1	3	50.0

CLS Capillary Leak Syndrome, TTO Time to Onset.

For the 28 cases, the event outcomes were reported as follows: 4 (14%) with fatal outcome, 5 (18%) were not recovered, 4 (14%) were recovered, 1 (4%) was recovered with sequelae, 6 (21%) were recovering and 8 (29%) events were with unknown outcome.

Amongst the 28 events, 4 were fatal. Case ID: PPD . The complete information on these cases were described in the cumulative definitive/probable CLS section above.

Among all 28 cases, there were cases that had relevant risk factors for CLS in the medical history such as: prior CLS (2), diabetes mellitus (3), hypergammaglobulinaemia benign monoclonal (2), immunodeficiency/infection/surgery (2), cardiac insufficiency (1), cardiac arrest (1), cardiogenic shock (1) and cardiac failure (1). Most of the cases had limited information with respect to medical history and concomitant medication (19 cases).

AstraZeneca assessed WHO-UMC causality for each of the 28 cases of CLS using a risk window of 0-7 days. Amongst 28 cases, 8 cases were identified within the TTO of 0-7 days and WHO-UMC causality was considered as possible. However, 4 cases were noted with confounding risk factors as follows: CLS (1), diabetes mellitus (1), hypergammaglobulinaemia benign monoclonal (2), cardiac insufficiency (1), cardiogenic shock (1), cardiac arrest (1), cardiac failure (1). In the remaining 4 cases, the information was limited on the medical history, concomitant medications and etiologic and diagnostic work up.

Amongst 28 cases, for 14 cases the TTO was unknown hence WHO-UMC was considered as unassessable/unclassifiable. However, 3 cases were noted with risk factors as follows: CLS (1), diabetes (1) and immunodeficiency/infection/surgery (1). In the remaining 11 cases the information was limited on the medical history, concomitant medications and etiologic and diagnostic work up.

Observed vs. Expected Analysis

Taking into account the very few case reports of Capillary leak syndrome and associated terms in the literature it is not possible to complete an observed vs. expected analysis for this concept as reliable background rates could not be identified. Approximately 500 reports of CLS in the general population during the pre-pandemic period have been reported in the literature (Druey et al 2017). AstraZeneca continues to work on new methods to retrieve incidence rates of CLS in the pandemic period.

Literature

AstraZeneca completed a search of the literature to identify any articles in Embase, InsightMeme, and PubMed published from 29 December 2020 through 28 December 2021 (covering both the cumulative and interval periods) to identify potential mechanisms of action leading to CLS with COVID-19 vaccination, including COVID-19 VACCINE ASTRAZENECA.

The search yielded 85 articles, which were reviewed in detail, however none of the articles discussed conclusive mechanisms of action leading to CLS after COVID-19 vaccination.

In brief, rare cases of CLS are observed across the different COVID vaccine platforms, as well as in individuals infected with COVID-19. Greinacher et al 2021 (Blood) proposed a mechanism of induction of CLS whereby the ChAdOx1 nCoV-19 vaccine contains EDTA, with the capacity for increasing capillary leakage at the inoculation site by a VE-cadherin-dependent pathway, however no data are available to support this hypothesis, nor has a definitive link between vaccines and CLS been established.

To date, no conclusive mechanism of action leading to CLS after COVID-19 vaccination has been identified. Furthermore, the mechanism as applicable to COVID-19 VACCINE ASTRAZENECA remains unclear.

Summary

This review presented cumulative and periodic data on CLS and related terms from all AZD1222 post-marketing safety case reports currently available to AstraZeneca.

There are 46 and 28 cases for the cumulative and interval period respectively assessed by AstraZeneca as meeting WHO-UMC criteria for Definitive/Probable CLS cases. However, medical review found that these cases had limited information or were confounded by alternative aetiologies including the possibility of a concurrent CLS and other risk factors. No abnormal trends or significant safety concerns were identified in the interval period with respect to the cumulative period. To date, no conclusive mechanism of action leading to CLS

after COVID-19 vaccination has been identified. Furthermore, the mechanism as applicable to COVID-19 VACCINE ASTRAZENECA remains unclear.

Conclusion

Based on available data as of 29 December 2021, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and CLS. No update to the core product information or RMP is warranted.

AstraZeneca will continue to monitor safety data of CLS and related terms from all available sources as part of routine safety surveillance for COVID-19 VACCINE ASTRAZENECA.

15.2.7 Cerebrovascular Events

Request

AstraZeneca received the following requests from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

"As during the assessment of MSSR07, a signal of CVST without thrombocytopenia was raised, the MAH is requested to include separate O/E analyses of CVST, pulmonary embolism, DVT and cerebrovascular events, including only observed cases in whom thrombocytopenia has not been reported."

AstraZeneca's response to these requests is provided below.

Case identification

A cumulative search of the AstraZeneca safety database was undertaken for adverse event (AE) reports for following PTs from the HLT of "Central nervous system vascular disorders" in association with the use of COVID-19 VACCINE ASTRAZENECA: Basal ganglia haematoma; Basal ganglia haemorrhage; Basal ganglia infarction; Basal ganglia stroke; Basilar artery occlusion; Basilar artery perforation; Basilar artery thrombosis; Benedikt's syndrome; Brain stem embolism; Brain stem haematoma; Brain stem haemorrhage; Brain stem infarction; Brain stem ischaemia; Brain stem stroke; Brain stem thrombosis; Carotid aneurysm rupture; Carotid arterial embolus; Carotid artery occlusion; Carotid artery perforation; Carotid artery thrombosis; Central nervous system haemorrhage; Cerebellar artery occlusion; Cerebellar artery thrombosis; Cerebellar embolism; Cerebellar haematoma; Cerebellar haemorrhage; Cerebellar infarction; Cerebellar ischaemia; Cerebellar stroke; Cerebral aneurysm perforation; Cerebral arteriovenous malformation haemorrhagic; Cerebral artery embolism; Cerebral artery occlusion; Cerebral artery perforation; Cerebral artery thrombosis; Cerebral gas embolism; Cerebral haematoma; Cerebral haemorrhage; Cerebral haemorrhage foetal; Cerebral infarction; Cerebral infarction foetal; Cerebral ischaemia;

Cerebral microembolism; Cerebral microinfarction; Cerebral septic infarct; Cerebral thrombosis; Cerebral vascular occlusion; Cerebrovascular accident; Claude's syndrome; Embolic cerebellar infarction; Embolic cerebral infarction; Embolic stroke; Extraischaemic cerebral haematoma; Haemorrhage intracranial; Haemorrhagic cerebellar infarction; Haemorrhagic cerebral infarction; Haemorrhagic stroke; Haemorrhagic transformation stroke; Inner ear infarction; Internal capsule infarction; Intracranial haematoma; Intracranial tumour haemorrhage; Intraoperative cerebral artery occlusion; Intraventricular haemorrhage; Ischaemic cerebral infarction; Ischaemic stroke; Lacunar infarction; Lacunar stroke; Lateral medullary syndrome; Meningorrhagia; Migrainous infarction; Perinatal stroke; Pituitary apoplexy; Pituitary haemorrhage; Pituitary infarction; Post procedural stroke; Post stroke depression; Precerebral artery embolism; Precerebral artery occlusion; Precerebral artery thrombosis; Pseudo-occlusion of internal carotid artery; Pseudostroke; Putamen haemorrhage; Reversible ischaemic neurological deficit; Ruptured cerebral aneurysm; Septic cerebral embolism; Stroke in evolution; Subarachnoid haematoma; Subarachnoid haemorrhage; Thalamic infarction; Thalamus haemorrhage; Thrombotic cerebral infarction; Thrombotic stroke; Weber's syndrome". This covered the period up to 28 December 2021 and only closed cases were included in the search. The case reports of CVST without thrombocytopenia and Thrombosis in combination with thrombocytopenia (including CVST with thrombocytopenia) were excluded.

The search resulted in a total of 4,962 individual closed cases (cumulative up to 28 December 2021); out of 4962 cases, 523 were reported as Thrombosis in combination with thrombocytopenia (including CVST with thrombocytopenia) and 74 were reported as CVST without thrombocytopenia reports. Hence the analysis is focused on 4365 case reports.

Incidence Rate Selection

The 'Incidence Rate (IR)' for the cerebrovascular events is derived through medical review and assessment of published literature or epidemiologic program outcome data that most accurately reflects the background rate for the exposed population. The justifications for the literature search are provided below in Table 37:

Table 37 Literature Searches

Articles reviewed	• doi: 10.1136/bmjopen-2011-000269 • https://doi.org/10.1016/S1474-4422(21)00252-0 • doi: 10.1016/S2468-2667(18)30030-6 • doi: 10.1371/journal.pmed.1002669 • doi: 10.1016/S2468-2667(18)30030-6 • doi: 10.1016/S0140-6736(05)67702-1 • doi: 10.1161/01.STR.20.3.333 • DOI: 10.1177/1747493020909545 • DOI: 10.1161/CIRCRESAHA.116.308413 • DOI: 10.1159/000506396 • https://www.gov.uk/government/publications/first-stroke-estimates-in-england-2007-to-2016 • doi: 10.1136/jnnp.2007.117655 • https://doi.org/10.1161/STROKEAHA.120.029606 • doi: 10.1136/bmj.n1435
Article Selected	Akyea et al 2021 (doi: 10.1161/STROKEAHA.120.031659)
Incidence number (overall stroke)	109.21
Unit	100,000 person-years
Year of IR	1998-2017
Setting	Patients aged ≥18 years with a first record of nonfatal stroke in CPRD GOLD or HES between January 1998 and December 2018. Patients with prior history of stroke and <12 months of baseline registration were excluded.
Follow-up period	January 1998 – December 2017; total follow-up time of 75,794,468.8 person-years
Data source	Clinical Practice Research Datalink (CPRD) GOLD and Hospital Episode Statistics (HES)
Number of people observed	9,992,380 individuals aged ≥18 years in CPRD GOLD
Comments/Notes	As most of the case reports were from UK, this article was selected Study used primary care and hospital data so out-of-hospital events were more likely to be captured. Patients in CPRD are broadly representative of the UK general population in terms of sex, age, and ethnicity. HES is a national database with dates and diagnostic codes for all elective and emergency admissions and procedures to NHS hospitals in England. Study relied on clinical codes indicative of stroke so case ascertainment is a potential limitation, but the data quality is still believed to be high.
Reference (doi)	doi: 10.1161/STROKEAHA.120.031659

CPRD Clinical Practice Research Datalink, HES Hospital Episode Statistics, NHS National Health Service, UK United Kingdom.

For stroke sub-classification incidence rates from GBD 2021 were considered.

All cases were stratified by risk window of 28 and 42 days including and excluding cases with unknown time to onset. Stratification by age is performed for case reports from EEA and stratification by age and gender is performed for cases from the UK.

Observed versus Expected Analysis Summary

O/E analysis for cerebrovascular events are presented in Table 38. The observed versus expected analysis for all reported cases of cerebrovascular events with TTO within 28 days, and 42 days from vaccination suggested that observed cases are significantly less than expected (Table 38). When cases with an unknown time to onset are included as a conservative approach, observed cases are less than expected for all risk windows, apart from the 28 day risk window for All Stroke in Female Aged to 30 to 39 from UK (Observed significantly > expected) and with 28 days and 42 days for vaccinees ages <40 years from UK (male and female). However, most of the cases reported from the UK did not have sufficient information to do a causality assessment. Also, study by Patone et al 2021 suggested that there was no increased risk of haemorrhagic stroke and Subarachnoid hemorrhage with AZD1222 administration in the UK.

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke RW28	28	109.21	291626957	2267	24415.57	0.09 (0.09 - 0.1)	Observed significantly < expected
All Stroke RW42	42	109.21	291626957	2535	36623.35	0.07 (0.07 - 0.07)	Observed significantly < expected
All Stroke inc. Unk RW28	28	109.21	291626957	3699	24415.57	0.15 (0.15 - 0.16)	Observed significantly < expected
All Stroke inc. Unk RW42	42	109.21	291626957	3967	36623.35	0.11 (0.1 - 0.11)	Observed significantly < expected
Ischaemic Stroke RW28	28	94.51	291626957	1963	21129.16	0.09 (0.09 - 0.1)	Observed significantly < expected
Ischaemic Stroke RW42	42	94.51	291626957	2195	31693.73	0.07 (0.07 - 0.07)	Observed significantly < expected
Ischaemic Stroke inc. Unk RW28	28	94.51	291626957	3172	21129.16	0.15 (0.14 - 0.16)	Observed significantly < expected
Ischaemic Stroke inc. Unk RW42	42	94.51	291626957	3404	31693.73	0.11 (0.1 - 0.11)	Observed significantly < expected
Intracerebral haemorrhage RW28	28	41.81	291626957	297	9347.27	0.03 (0.03 - 0.04)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Intracerebral haemorrhage RW42	42	41.81	291626957	334	14020.9	0.02 (0.02 - 0.03)	Observed significantly < expected
Intracerebral haemorrhage inc. Unk RW28	28	41.81	291626957	494	9347.27	0.05 (0.05 - 0.06)	Observed significantly < expected
Intracerebral haemorrhage inc. Unk RW42	42	41.81	291626957	531	14020.9	0.04 (0.03 - 0.04)	Observed significantly < expected
Subarachnoid haemorrhage RW28	28	14.46	291626957	69	3232.75	0.02 (0.02 - 0.03)	Observed significantly < expected
Subarachnoid haemorrhage RW42	42	14.46	291626957	77	4849.13	0.02 (0.01 - 0.02)	Observed significantly < expected
Subarachnoid haemorrhage inc. Unk RW28	28	14.46	291626957	121	3232.75	0.04 (0.03 - 0.04)	Observed significantly < expected
Subarachnoid haemorrhage	42	14.46	291626957	129	4849.13	0.03 (0.02 - 0.03)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
inc. Unk RW42							
All Stroke-EU-18-49	28	26.07	27716022	120	553.92	0.22 (0.18 - 0.26)	Observed significantly < expected
All Stroke-EU-50-59	28	119.65	19552392	170	1793.45	0.09 (0.08 - 0.11)	Observed significantly < expected
All Stroke-EU-60-69	28	257.93	28510714	432	5637.50	0.08 (0.07 - 0.08)	Observed significantly < expected
All Stroke-EU-70-79	28	494.26	14795684	326	5606.18	0.06 (0.05 - 0.06)	Observed significantly < expected
All Stroke-EU-80+	28	784.66	3858135	108	2320.79	0.05 (0.04 - 0.06)	Observed significantly < expected
All Stroke-EU-All ages	28	109.21	68948629	1183	5772.51	0.2 (0.19 - 0.22)	Observed significantly < expected
All Stroke-EU-18-49	42	26.07	27716022	136	830.88	0.16 (0.14 - 0.19)	Observed significantly < expected
All Stroke-EU-50-59	42	119.65	19552392	193	2690.18	0.07 (0.06 - 0.08)	Observed significantly < expected
All Stroke-EU-60-69	42	257.93	28510714	479	8456.25	0.06 (0.05 - 0.06)	Observed significantly < expected
All Stroke-EU-70-79	42	494.26	14795684	348	8409.27	0.04 (0.04 - 0.05)	Observed significantly < expected
All Stroke-EU-80+	42	784.66	3858135	115	3481.18	0.03 (0.03 - 0.04)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke-EU-All ages	42	109.21	68948629	1299	8658.77	0.15 (0.14 - 0.16)	Observed significantly < expected
All Stroke Male-All ages-UK	28	102.36	23980140	406	1881.74	0.22 (0.2 - 0.24)	Observed significantly < expected
All Stroke Male-All ages-UK	42	102.36	23980140	472	2822.60	0.17 (0.15 - 0.18)	Observed significantly < expected
All Stroke Female-All ages-UK	28	115.84	24872206	360	2208.77	0.16 (0.15 - 0.18)	Observed significantly < expected
All Stroke Female-All ages-UK	42	115.84	24872206	411	3313.15	0.12 (0.11 - 0.14)	Observed significantly < expected
All Stroke-UK--Male Aged-20-29	28	7.21	986375	3	5.45	0.55 (0.11 - 1.61)	Observed < expected
All Stroke-UK--Male Aged-30-39	28	21.57	1582807	16	26.17	0.61 (0.35 - 0.99)	Observed significantly < expected
All Stroke-UK--Male Aged-40-49	28	59.62	5220928	34	238.63	0.14 (0.1 - 0.2)	Observed significantly < expected
All Stroke-UK--Male Aged-50-59	28	139.5	6957211	111	744.02	0.15 (0.12 - 0.18)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke-UK--Male Aged-60-69	28	276.66	4966917	88	1053.44	0.08 (0.07 - 0.1)	Observed significantly < expected
All Stroke-UK--Male Aged-70-79	28	487.07	3223317	84	1203.57	0.07 (0.06 - 0.09)	Observed significantly < expected
All Stroke-UK--Male Aged-80+	28	708.79	1042292	40	566.35	0.07 (0.05 - 0.1)	Observed significantly < expected
All Stroke-UK--Female Aged-20-29	28	7.75	1339334	5	7.96	0.63 (0.2 - 1.47)	Observed < expected
All Stroke-UK--Female Aged-30-39	28	17.33	2096348	12	27.85	0.43 (0.22 - 0.75)	Observed significantly < expected
All Stroke-UK--Female Aged-40-49	28	40.13	4974220	51	153.03	0.33 (0.25 - 0.44)	Observed significantly < expected
All Stroke-UK--Female Aged-50-59	28	99.89	6319086	64	483.90	0.13 (0.1 - 0.17)	Observed significantly < expected
All Stroke-UK--Female Aged-60-69	28	241.39	4859019	65	899.18	0.07 (0.06 - 0.09)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke-UK--Female Aged-70-79	28	499.3	3562147	82	1363.48	0.06 (0.05 - 0.07)	Observed significantly < expected
All Stroke-UK--Female Aged-80+	28	817.72	1721795	48	1079.35	0.04 (0.03 - 0.06)	Observed significantly < expected
All Stroke-UK--Male Aged-20-29	42	7.21	986375	4	8.18	0.49 (0.13 - 1.25)	Observed < expected
All Stroke-UK--Male Aged-30-39	42	21.57	1582807	22	39.26	0.56 (0.35 - 0.85)	Observed significantly < expected
All Stroke-UK--Male Aged-40-49	42	59.62	5220928	44	357.94	0.12 (0.09 - 0.17)	Observed significantly < expected
All Stroke-UK--Male Aged-50-59	42	139.5	6957211	126	1116.03	0.11 (0.09 - 0.13)	Observed significantly < expected
All Stroke-UK--Male Aged-60-69	42	276.66	4966917	104	1580.16	0.07 (0.05 - 0.08)	Observed significantly < expected
All Stroke-UK--Male Aged-70-79	42	487.07	3223317	95	1805.35	0.05 (0.04 - 0.06)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke-UK--Male Aged-80+	42	708.79	1042292	44	849.52	0.05 (0.04 - 0.07)	Observed significantly < expected
All Stroke-UK--Female Aged-20-29	42	7.75	1339334	5	11.94	0.42 (0.14 - 0.98)	Observed significantly < expected
All Stroke-UK--Female Aged-30-39	42	17.33	2096348	13	41.78	0.31 (0.17 - 0.53)	Observed significantly < expected
All Stroke-UK--Female Aged-40-49	42	40.13	4974220	57	229.54	0.25 (0.19 - 0.32)	Observed significantly < expected
All Stroke-UK--Female Aged-50-59	42	99.89	6319086	74	725.85	0.1 (0.08 - 0.13)	Observed significantly < expected
All Stroke-UK--Female Aged-60-69	42	241.39	4859019	73	1348.76	0.05 (0.04 - 0.07)	Observed significantly < expected
All Stroke-UK--Female Aged-70-79	42	499.3	3562147	98	2045.23	0.05 (0.04 - 0.06)	Observed significantly < expected
All Stroke-UK--Female Aged-80+	42	817.72	1721795	52	1619.03	0.03 (0.02 - 0.04)	Observed significantly < expected
All Stroke EU 18 to 49	28	26.07	27716022	155	553.92	0.28 (0.24 - 0.33)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
inc. Unk TTO RW28							
All Stroke EU 50 to 59 inc. Unk TTO RW28	28	119.65	19552392	182	1793.45	0.1 (0.09 - 0.12)	Observed significantly < expected
All Stroke EU 60 to 69 inc. Unk TTO RW28	28	257.93	28510714	468	5637.5	0.08 (0.08 - 0.09)	Observed significantly < expected
All Stroke EU 70 to 79 inc. Unk TTO RW28	28	494.26	14795684	341	5606.18	0.06 (0.05 - 0.07)	Observed significantly < expected
All Stroke EU 80 plus inc. Unk TTO RW28	28	784.66	3858135	119	2320.79	0.05 (0.04 - 0.06)	Observed significantly < expected
All Stroke EU All ages inc. Unk TTO RW28	28	109.21	68948629	1345	5772.51	0.23 (0.22 - 0.25)	Observed significantly < expected
All Stroke EU 18 to 49 inc. Unk TTO RW42	42	26.07	27716022	171	830.88	0.21 (0.18 - 0.24)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke EU 50 to 59 inc. Unk TTO RW42	42	119.65	19552392	205	2690.18	0.08 (0.07 - 0.09)	Observed significantly < expected
All Stroke EU 60 to 69 inc. Unk TTO RW42	42	257.93	28510714	515	8456.25	0.06 (0.06 - 0.07)	Observed significantly < expected
All Stroke EU 70 to 79 inc. Unk TTO RW42	42	494.26	14795684	363	8409.27	0.04 (0.04 - 0.05)	Observed significantly < expected
All Stroke EU 80 plus inc. Unk TTO RW42	42	784.66	3858135	126	3481.18	0.04 (0.03 - 0.04)	Observed significantly < expected
All Stroke EU All ages inc. Unk TTO RW42	42	109.21	68948629	1461	8658.77	0.17 (0.16 - 0.18)	Observed significantly < expected
All Stroke male All ages UK inc. Unk TTO RW28	28	102.36	23980140	693	1881.74	0.37 (0.34 - 0.4)	Observed significantly < expected
All Stroke male All	42	102.36	23980140	759	2822.6	0.27 (0.25 - 0.29)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
ages UK inc. Unk TTO RW42							
All Stroke Female All ages UK inc. Unk TTO RW28	28	115.84	24872206	778	2208.77	0.35 (0.33 - 0.38)	Observed significantly < expected
All Stroke Female All ages UK inc. Unk TTO RW42	42	115.84	24872206	829	3313.15	0.25 (0.23 - 0.27)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 20 to 29 RW28	28	7.21	986375	6	5.45	1.1 (0.4 - 2.4)	Observed > expected
All Stroke UK inc. Unk TTO Male Aged to 30 to 39 RW28	28	21.57	1582807	21	26.17	0.8 (0.5 - 1.23)	Observed < expected
All Stroke UK inc. Unk TTO Male	28	59.62	5220928	79	238.63	0.33 (0.26 - 0.41)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Aged to 40 to 49 RW28							
All Stroke UK inc. Unk TTO Male Aged to 50 to 59 RW28	28	139.5	6957211	184	744.02	0.25 (0.21 - 0.29)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 60 to 69 RW28	28	276.66	4966917	142	1053.44	0.13 (0.11 - 0.16)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 70 to 79 RW28	28	487.07	3223317	117	1203.57	0.1 (0.08 - 0.12)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 80 plus RW28	28	708.79	1042292	61	566.35	0.11 (0.08 - 0.14)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 20 to 29 RW28	28	7.75	1339334	13	7.96	1.63 (0.87 - 2.79)	Observed > expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke UK inc. Unk TTO Female Aged to 30 to 39 RW28	28	17.33	2096348	41	27.85	1.47 (1.06 - 2)	Observed significantly > expected
All Stroke UK inc. Unk TTO Female Aged to 40 to 49 RW28	28	40.13	4974220	127	153.03	0.83 (0.69 - 0.99)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 50 to 59 RW28	28	99.89	6319086	169	483.9	0.35 (0.3 - 0.41)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 60 to 69 RW28	28	241.39	4859019	141	899.18	0.16 (0.13 - 0.18)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 70 to 79 RW28	28	499.3	3562147	143	1363.48	0.1 (0.09 - 0.12)	Observed significantly < expected
All Stroke UK inc. Unk	28	817.72	1721795	60	1079.35	0.06 (0.04 - 0.07)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTO Female Aged to 80 plus RW28							
All Stroke UK inc. Unk TTO Male Aged to 20 to 29 RW42	42	7.21	986375	7	8.18	0.86 (0.34 - 1.76)	Observed < expected
All Stroke UK inc. Unk TTO Male Aged to 30 to 39 RW42	42	21.57	1582807	27	39.26	0.69 (0.45 - 1)	Observed < expected
All Stroke UK inc. Unk TTO Male Aged to 40 to 49 RW42	42	59.62	5220928	89	357.94	0.25 (0.2 - 0.31)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 50 to 59 RW42	42	139.5	6957211	199	1116.03	0.18 (0.15 - 0.2)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male	42	276.66	4966917	158	1580.16	0.1 (0.09 - 0.12)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Aged to 60 to 69 RW42							
All Stroke UK inc. Unk TTO Male Aged to 70 to 79 RW42	42	487.07	3223317	128	1805.35	0.07 (0.06 - 0.08)	Observed significantly < expected
All Stroke UK inc. Unk TTO Male Aged to 80 plus RW42	42	708.79	1042292	65	849.52	0.08 (0.06 - 0.1)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 20 to 29 RW42	42	7.75	1339334	13	11.94	1.09 (0.58 - 1.86)	Observed > expected
All Stroke UK inc. Unk TTO Female Aged to 30 to 39 RW42	42	17.33	2096348	42	41.78	1.01 (0.72 - 1.36)	Observed > expected
All Stroke UK inc. Unk TTO Female Aged to 40 to 49 RW42	42	40.13	4974220	133	229.54	0.58 (0.49 - 0.69)	Observed significantly < expected

Table 38 O/E Analysis for Cerebrovascular Events

Topic Description	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All Stroke UK inc. Unk TTO Female Aged to 50 to 59 RW42	42	99.89	6319086	179	725.85	0.25 (0.21 - 0.29)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 60 to 69 RW42	42	241.39	4859019	149	1348.76	0.11 (0.09 - 0.13)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 70 to 79 RW42	42	499.3	3562147	159	2045.23	0.08 (0.07 - 0.09)	Observed significantly < expected
All Stroke UK inc. Unk TTO Female Aged to 80 plus RW42	42	817.72	1721795	64	1619.03	0.04 (0.03 - 0.05)	Observed significantly < expected

TTO Time to Onset, UK United Kingdom

Conclusion

Information from this cumulative O/E analysis did not find evidence of a new or emerging signal regarding cerebrovascular events (excluding CVST and TTS) and COVID-19 VACCINE ASTRAZENECA. No changes to the CDS or RMP are recommended. Cerebrovascular events will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

15.2.8 Deep vein thrombosis (DVT) without thrombocytopenia

Request

In the AR for the 8th SSR (review period: 01 October 2021 – 30 November 2021), AstraZeneca identified the following comment from PRAC:

"This topic [Deep vein thrombosis (DVT) without thrombocytopenia] will continue to be monitored in the upcoming PSURs."

AstraZeneca as provided an updated cumulative review of DVT without thrombocytopenia below.

Review of Cases

A cumulative search of the AstraZeneca global safety database was undertaken for AE reports received for COVID-19 VACCINE ASTRAZENECA through 28 December 2021 containing the following MedDRA PTs: Axillary vein thrombosis, Deep vein thrombosis, Jugular vein embolisms, Jugular vein thrombosis, Paget-Schoettler syndrome, Pelvic venous thrombosis, Penile vein thrombosis, Peripheral embolism, Peripheral vein thrombus extension, Subclavian vein thrombosis, Superficial vein thrombosis, Thrombophlebitis, Thrombosis corpora cavernosa and Venous thrombosis limb.

A total of 5883 cases were identified using the above search strategy.

To identify the cases of DVT without co-reported thrombocytopenia, the following were excluded from the search results described above: any cases with events from the HLT "Thrombocytopenias", SMQ "Hematopoietic thrombocytopenia (Narrow)", or cases with platelet values less than 150,000 per microliter.

After applying the exclusion criteria, 5407 cases of DVT without thrombocytopenia remained for further analysis.

The reported DVT PTs from the 5407 cases were (one case may contain >1 PT): Deep vein thrombosis (4003), Superficial vein thrombosis (752), Thrombophlebitis (636), Venous thrombosis limb (267), Jugular vein thrombosis (45), Pelvic venous thrombosis (41), Peripheral embolism (36), Subclavian vein thrombosis (31), Axillary vein thrombosis (10), Penile vein thrombosis (7), Paget-Schroetter syndrome (2) and Peripheral vein thrombus extension (2).

Of the 5407 case reports, 4816 (89%) were reported as serious and 591 (11%) were reported as non-serious and 2875 were medically confirmed. The reported seriousness criteria for the 4816 serious cases of DVT without thrombocytopenia included: Death (93), Life-threatening (590), Hospitalization or prolongation of existing hospitalization (1491), Persistent or significant disability or incapacity (234), Congenital anomaly (3) and Medically significant (3706). A single case may have met more than one criteria for seriousness.

Of the 5407 cases, 1401 (25.9%) were reported from UK and 1149 (21.3%) were reported from Australia. A total of 2963 (54.8%) case reports were reported in females, 2351 (43.5%) were reported in males, and in 93 (1.7%) the gender was not reported. Out of 5407 reported cases, 2911 (53.8%) occurred in adults (18-64 years of age) with median age of 53 years, 2153 (39.8%) in elderly (≥ 65 years of age) with median age 73 years, and in 343 (6.3%) the age was not reported. In the age group of 18-49 years, out of 1098 cases, 720 (65.6%) cases were reported in females. The median age was 63 years (for all cases; range 18 to 105 years).

Of the 5407 case reports, 93 (1.7%) cases reported a fatal outcome. Of the 93 cases reported with a fatal outcome, 52 were medically confirmed cases and 41 were non-medically confirmed. Of the 93 fatal cases, 9 (9.7%) occurred in the age group of 18-49. Age/gender and percentage of the total cases for the fatal reports is presented in Table 39.

Table 39 DVT Without Thrombocytopenia Case Reports by age/gender, and fatality

Age group	**Female N (Fatal cases) Fatal%**	**Male N (**Fatal cases) Fatal%	**Gender Unknown N (Fatal** cases) Fatal%	**Total N (Fatal cases) Fatal%**
Age - 18-29 Years	95 (0) 0%	29 (0) 0%	1 (0) 0%	125 (0) 0%
Age - 30-39 Years	215 (2) 0.9%	106 (1) 0.9%	2 (0) 0%	323 (3) 0.9%
Age - 40-49 Years	404 (4) 1.0%	227 (2) 0.9%	11 (0) 0%	642 (6) 0.9%
Age - 50-59 Years	504 (5) 1.0%	471 (9) 1.9%	10 (0) 0%	985 (14) 1.4%
Age - 60-69 Years	762 (11) 1.4%	731 (13) 1.8%	17 (0) 0%	1510 (24) 1.6%
Age - 70-79 Years	560 (18) 3.2%	512 (6) 1.2%	10 (0) 0%	1082 (24) 2.2%
Age - 80+ Years	250 (11) 4.4%	144 (5) 3.5%	3 (0) 0%	397 (16) 4.0%
Age Unknown	173 (2) 1.2%	131 (4) 3.1%	39 (0) 0%	343 (6) 1.7%
Grand Total	2963 (53) 1.8%	2351 (40) 1.7%	93 (0) 0%	5407 (93) 1.7%

N Number of cases

The most common (>2) reported cause(s) of death in the 93 fatal reports in order of frequency were Pulmonary embolism (62), Deep vein thrombosis (61), Cardiac arrest (4), and Venous thrombosis limb (3). The most common (>2) reported causes of death in 18 to 49 age group was: Pulmonary embolism (7), and Deep vein thrombosis (7).

Medical history information was available for 55 out of the 93 fatal reports. Risk and confounding factors included the following: hypertension (11), asthma (8), deep vein

thrombosis (6), depression (6), obesity (6), type 2 diabetes mellitus (6), dementia (5), arteriosclerosis (4), osteoarthritis (4), suspected Covid-19 (4), cardiac failure (3), tobacco user (3), hypothyroidism (3), thrombocytopenia (2), dyspnoea exertional (2), suicide attempt (2), cerebrovascular accident (2), varicose vein (2), asthenia (2), pulmonary embolism (2), arteriosclerosis coronary artery (2), immobile (2), ex-tobacco user (2), hepatic steatosis (2), rectal cancer (2), irritable bowel syndrome (2), cellulitis (1), cerebral palsy (2), sleep apnoea syndrome (1), lung neoplasm malignant (1), aortic aneurysm (1), pancreatitis acute (1), chemotherapy (1), chest pain (1), stress fracture (1), knee operation (1), myocardial infarction (1), chronic obstructive pulmonary disease (1), chronic kidney disease (1), pulmonary endarterectomy (1), rheumatoid arthritis (1), colitis ulcerative (1), cast application (1), colostomy (1), coronary artery bypass (1), acute myocardial infarction (1), alcoholic (1), deficiency anaemia (1), Parkinson's disease (1), prostate cancer (1), renal hypertrophy (1), diabetic nephropathy (1), disability (1), squamous cell carcinoma of skin (1), ankle fracture (1), endocarditis (1), knee arthroplasty (1), epilepsy (1), lumbar vertebral fracture (1), atrial septal defect (1), myocardial ischaemia (1), fall (1), breast cancer (1), fracture (1), bronchopneumopathy (1), ovarian cancer (1), gastrointestinal carcinoma (1), pelvic fracture (1), haemorrhage (1), peripheral venous disease (1), haemorrhoids (1), basal cell carcinoma (1), anticoagulant therapy (1), radiotherapy (1), vascular dementia (1), hydrocephalus (1), retroperitoneal cancer (1), hypercholesterolaemia (1), right ventricular hypertrophy (1), hypertensive heart disease (1), small intestinal obstruction (1), hypopituitarism (1), steroid therapy (1), ileostomy (1), substance dependence (1), brain injury (1), immunodeficiency (1), inflammation (1), cerebral haemorrhage (1), varicose vein (1), hepatic cirrhosis (1), ventriculo-pleural shunt (1), hepatitis (1), and humerus fracture (1).

One case may have more than one risk/confounding factor.

Reported outcomes in the remaining 5314 non-fatal case reports of DVT without thrombocytopenia were: Not Recovered 1915 (35.4%), Recovered 490 (9.1%), Recovering 1993 (36.9%), Recovered With Sequelae 105 (1.9%), and Unknown/missing 811 (15.0%).

The time to onset from the administration of vaccine to the onset of the DVT event was available in 4574 (84.6%) case reports. The time to onset from the administration of vaccine to the event onset was 0-7 days in 1857 (34.3%), 8-14 days in 956 (17.7%), 15-21 days in 556 (10.3%), 22-28 days in 370 (6.8%), and greater than 28 days in 835 (15.4%) of cases. Time to onset ranged from 0 – 243 days with a median of 11 days.

There was available information on confounding comorbidities, other medical confounders or risk factors, and confounding medications reported in 2420 (44.8%) of the 5407 cases.

Among those reports that included medical history information, risk/confounding factors included the following: hypertension (506), deep vein thrombosis (311), type 2 diabetes mellitus (232), obesity (159), cases with past history of heparin suggesting history of thrombotic events (151), asthma (122), tobacco user (115), varicose vein (111), suspected covid-19 (98), pulmonary embolism (97), hypothyroidism (78), hypercholesterolaemia (74), osteoarthritis (73), thrombophlebitis (69), hypersensitivity (69), thrombosis (67), depression

(67), peripheral venous disease (66), covid-19 (61), breast cancer (59), dyslipidaemia (57), rheumatoid arthritis (54), superficial vein thrombosis (44), pulmonary disease (42), sleep apnoea syndrome (39), phlebitis (39), cerebrovascular accident (36), surgery (35), immunodeficiency (33), steroid therapy (32), overweight (31), drug seasonal allergy (30), atrial fibrillation (30), osteoporosis (29), pain in extremity (28), factor v leiden mutation (27), prostate cancer (27), neoplasm malignant (26), myocardial infarction (23), gout (23), neoplasm (23), hyperlipidaemia (23), migraine (22), transient ischaemic attack (22), chronic kidney disease (18), pregnancy (18), hyperuricaemia (17), chronic obstructive dyspnoea (17), anxiety (17), fibromyalgia (16), arthritis (16), varicose vein operation (15), psoriasis (15), headache (15), myocardial ischaemia (15), dementia (14), hip arthroplasty (14), chest pain (13), sciatica (13), pneumonia (13), arthralgia (13), arthroscopy (13), nephrectomy (12), hepatic steatosis (12), fall (12), epilepsy (12), diverticulum (12), colitis (12), back pain (11), phlebectomy (11), cellulitis (11), knee arthroplasty (10), arrhythmia (10), splenectomy (10), fracture (10), spinal pain (9), hip arthroplasty (9), coronary artery disease (9), arteriosclerosis (9), venous thrombosis limb (8), embolism (8), osteopenia (8), joint prosthesis user (8), injury (8), goitre (8), alcoholism (7), Parkinson's disease (7), thrombocytopenia (7), venous thrombosis limb (7), hypercoagulation (7), knee arthroplasty (7), chemotherapy (9), hiatus hernia (9), mixed anxiety and depressive disorder (9), malignant melanoma (8), haemorrhoids (8), bronchiectasis (8), sarcoidosis (7), erysipelas (7), infection (7), food allergy (7), cholelithiasis (7), colitis ulcerative (7), cardiac failure (7), inguinal hernia (7), sclerotherapy (6), and radiotherapy (6).

Concomitant confounding medications included citalopram (40), amitriptyline[MG1] [PJ2] (37), sertraline (34), prednisolone (24), methotrexate (21), oestradiol (11), escitalopram (11), dexamethasone (6), quinine (5), hydrocortisone (5), mometasone (3), contraceptives (3), and oestrogen (2).

Additionally, possible confounding concurrent events included the following: influenzas (71), tachycardia (30), cellulitis (28), cardiac disorders (28), varicose veins (27), diarrhoea (27), hypertension (20), Covid-19 infection (17), infections (15), atrial fibrillation (13), hypotension (8), pregnancies (7), fall (7), fractures (6), arrythmias (5), cancers (5), dehydration (4), and hospitalization (3).

A single case may have more than one risk factor.

<u>DVT without thrombocytopenia events after 2nd dose of the vaccine</u>

There were 254 case reports of DVT without thrombocytopenia reported to have occurred following the second dose in individuals who were reported to have received 2 doses of COVID-19 VACCINE ASTRAZENECA. Age was reported for 214 case reports. In 185 (86.4%) of the case reports where age was reported and the event occurred post 2nd dose, the vaccinee was >50 years. Of the 254 reports, 135 (53.1%) were in females, and 117 (46.1%) in males, and gender was unknown for 2 (0.8%) reports. TTO after 2nd dose was reported as 0-7 days in 69 (27.3%) cases, 8-14 days in 40 (15.8%) cases, 15-21 days in 39 (15.4%) cases, 22-28 days in 30 (11.9%) cases, and >28 days in 75 (29.6%) cases.

There were 5 deaths out of 254 case reports. Details of these 5 fatal outcomes are provided in below Table 40. Age of the 5 vaccinees with a fatal outcome ranged from 49 to 82 with a median of 61 years.

Table 40 Patients with fatal DVT events after Dose 1 and Dose 2 (n = 5) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 JUNE 2021 – 28 DECEMBER 2021

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Deep vein thrombosis	UNK	UNK	Deep vein thrombosis	10	Died	PPD	UNK	The reported events deep vein thrombosis and multiple organ dysfunction syndrome could be in a possible association to each other. PPD could be a possible contributory risk factor for the events. Medical history of ulcerative colitis could be a possible confounder.
PPD	PPD	Deep vein thrombosis	UNK	UNK	Deep vein thrombosis	2	Died		UNK	
PPD	PPD	Deep vein thrombosis	UNK	UNK	Deep vein thrombosis	16	Died		PPD	Reported Cardiac arrest could be in association Deep vein thrombosis. Relevant medication history of PPD indicates thromboembolic event in past which could be confounding factor of Deep vein thrombosis.
PPD	PPD	Deep vein thrombosis	UNK	UNK	Deep vein thrombosis	31	Died		UNK	Reported events of Deep vein thrombosis , Pulmonary embolism and Fibrin D dimer increased could be in association with each other.
PPD	PPD	Deep vein thrombosis	UNK	UNK	Deep vein thrombosis	96	Died		UNK	Reported events of Deep vein thrombosis and pain in extremity could be in association with each other. PPD could be a risk factor for the event of Deep vein thrombosis

Unk, Unknown.

Among 254 cases reporting DVT events after the 2nd dose, medical history was available for 141 (55.5%) cases. The most frequently reported (≥3) risk/confounding factors were: hypertension (21), deep vein thrombosis (16), depression (11), asthma (9), tobacco user (9), obesity (7), suspected covid-19 (6), pulmonary embolism (6), breast cancer (6), hypercholesterolaemia (6), immunodeficiency (5), diabetes mellitus (5), cerebrovascular accident (5), varicose vein (5), rheumatoid arthritis (4), surgery (4), hypothyroidism (4), osteoarthritis (4), epilepsy (3), covid-19 (3), ex-tobacco user (3), sciatica (3), fibromyalgia (3), chronic kidney disease (3), thrombosis (3), alcohol abuse (3), hyperlipidaemia (3), and sleep apnoea syndrome (3). Some cases may have more than one risk/confounding factor.

Twenty-one (21) cases reported past drug use of heparin, suggesting a history of previous thrombotic events. Additionally, cases with concomitant confounding drugs (frequency ≥2) included sertraline (3), fexofenadine (3), cipralex (2), tamoxifen (2), citalopram (2), and mirtazapine (2).

Additionally, possible concurrent confounding adverse events included the following (frequency>2), were reported Covid-19 (6), contusion (4), pneumonia (4), vomiting (4), phlebitis superficial (3), tachycardia (3), arthralgia (3), myocardial infarction (2), vasculitis (2), mobility decreased (2), influenza like illness (2), cellulitis (2), gout (2), and asthenia (2).

There were 13 cases where a DVT event was reported to have occurred after both 1st and 2nd dose. Age was reported for 11 of the 13 cases and 9 patients were ≥50 years old (range 28-81 years, median 59 years). Of the 13 reports, 8 were in females, 4 were in males, and gender was unknown in 1 report. All 13 cases were reported from the UK. The reported events after 1st dose were Deep vein thrombosis (12) and Thrombophlebitis (1). TTO after 1st dose was only available for 1 of the 13 cases, and it was 3 days. Outcome after 1st dose for the 13 cases was unknown (5), recovering (5), not recovered (2), and recovered (1).

The reported events after 2nd dose were Deep vein thrombosis (12) and Thrombophlebitis (1). TTO after 2nd dose was reported for 12 cases as 0-7 days in 3 cases, 8-14 days in 2 cases, 15-21 days in 3 cases, 22-28 days in 2 cases, and 36 and 62 days respectively in 1 case each. Outcome after 2nd dose for the 13 cases was recovering (5), unknown (5), not recovered (2), and recovered (1).

Of the thirteen cases reporting DVT events after both 1st and 2nd doses, medical history information was available for 9. For those 9 cases, confounding/risk factors included the following: hip arthroplasty, fall, asthma, stasis dermatitis, ligament sprain, cellulitis, chronic kidney disease 2, immunodeficiency, thrombocytopenia, partial seizures, phospholipidosis, rheumatoid arthritis, steroid therapy, tobacco user, diabetes mellitus, sciatica, intervertebral disc degeneration, chronic obstructive pulmonary disease, bronchiectasis, cauda equina syndrome, urinary tract infection, diverticulitis, skin ulcer, and 3 out of 13 cases had past use of heparin suggesting previous thrombotic events.

Concomitant confounding drugs included the following: sertraline (2), fexofenadine (1), olanzapine (1), lercanidipine (1), amitriptyline (1), carbamazepine (1), estrogel (1), methotrexate (1), and prednisolone (1).

Additionally, possible concomitant events included the following: influenza like illness; cellulitis; iron deficiency anaemia; covid-19; and myocardial infarction.

DVT without thrombocytopenia events after 3rd dose of the vaccine

There was 1 case (PPD) where a DVT event was reported to have occurred after 3rd dose of the vaccine. A PPD year old PPD patient was hospitalised due to DVT 8 days after receiving 3rd dose of the vaccine. At the time of reporting the patient was improving. The patient's reported underlying medical history of PPD could be a confounding factor for DVT.

Observed vs. Expected Analysis

The observed versus expected analyses are carried out using incidence rates from Truven MarketScan (2019). These analyses are presented with 14, 28 and 42 risk window (this is the same risk window used for other thromboembolic events) for all global reports and stratified by age in the EEA and UK regions, and by age and gender in the UK. All stratifications are also included including cases with an unknown time to onset, as a conservative approach.

The O/E analysis results for DVT without TCP showed observed cases significantly less than expected for all stratifications (Table 41).

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	14	341.84	291626957	2283	38211.78	0.06 (0.06 - 0.06)	Observed significantly < expected
Overall (Global) with Unk TTO	14	341.84	291626957	2568	38211.78	0.07 (0.06 - 0.07)	Observed significantly < expected
Overall (Global)	28	341.84	291626957	2984	76423.56	0.04 (0.04 - 0.04)	Observed significantly < expected
Overall (Global) with Unk TTO	28	341.84	291626957	3296	76423.56	0.04 (0.04 - 0.04)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	42	341.84	291626957	3313	114635.34	0.03 (0.03 - 0.03)	Observed significantly < expected
Overall (Global) with Unk TTO	42	341.84	291626957	3598	114635.34	0.03 (0.03 - 0.03)	Observed significantly < expected
Female 18 to 29 UK	14	79.84	1339334	17	40.99	0.41 (0.24 - 0.66)	Observed significantly < expected
Female 30 to 39 UK	14	197.4	2096348	38	158.62	0.24 (0.17 - 0.33)	Observed significantly < expected
Female 40 to 49 UK	14	298.24	4974220	85	568.64	0.15 (0.12 - 0.18)	Observed significantly < expected
Female 50 to 59 UK	14	355.51	6319086	79	861.1	0.09 (0.07 - 0.11)	Observed significantly < expected
Female 60 to 69 UK	14	503.82	4859019	73	938.36	0.08 (0.06 - 0.1)	Observed significantly < expected
Female 70 to 79 UK	14	1143.08	3562147	51	1560.76	0.03 (0.02 - 0.04)	Observed significantly < expected
Female over 80 UK	14	1731.85	1721795	20	1142.98	0.02 (0.01 - 0.03)	Observed significantly < expected
Male 18 to 29 UK	14	49.13	986375.5	5	18.58	0.27 (0.09 - 0.63)	Observed significantly < expected
Male 30 to 39 UK	14	130.28	1582807	18	79.04	0.23 (0.13 - 0.36)	Observed significantly < expected
Male 40 to 49 UK	14	253.77	5220928	51	507.85	0.1 (0.07 - 0.13)	Observed significantly < expected
Male 50 to 59 UK	14	472.47	6957211	91	1259.96	0.07 (0.06 - 0.09)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 60 to 69 UK	14	705.7	4966917	80	1343.55	0.06 (0.05 - 0.07)	Observed significantly < expected
Male 70 to 79 UK	14	1219.14	3223317	49	1506.27	0.03 (0.02 - 0.04)	Observed significantly < expected
Male over 80 UK	14	1844.15	1042292	7	736.77	0.01 (0 - 0.02)	Observed significantly < expected
Female 18 to 29 UK	28	79.84	1339334	19	81.98	0.23 (0.14 - 0.36)	Observed significantly < expected
Female 30 to 39 UK	28	197.4	2096348	44	317.24	0.14 (0.1 - 0.19)	Observed significantly < expected
Female 40 to 49 UK	28	298.24	4974220	112	1137.28	0.1 (0.08 - 0.12)	Observed significantly < expected
Female 50 to 59 UK	28	355.51	6319086	112	1722.2	0.07 (0.05 - 0.08)	Observed significantly < expected
Female 60 to 69 UK	28	503.82	4859019	96	1876.73	0.05 (0.04 - 0.06)	Observed significantly < expected
Female 70 to 79 UK	28	1143.08	3562147	65	3121.51	0.02 (0.02 - 0.03)	Observed significantly < expected
Female over 80 UK	28	1731.85	1721795	32	2285.96	0.01 (0.01 - 0.02)	Observed significantly < expected
Male 18 to 29 UK	28	49.13	986375	6	37.15	0.16 (0.06 - 0.35)	Observed significantly < expected
Male 30 to 39 UK	28	130.28	1582807	26	158.08	0.16 (0.11 - 0.24)	Observed significantly < expected
Male 40 to 49 UK	28	253.77	5220928	71	1015.7	0.07 (0.05 - 0.09)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 50 to 59 UK	28	472.47	6957211	123	2519.92	0.05 (0.04-0.06)	Observed significantly < expected
Male 60 to 69 UK	28	705.7	4966917	101	2687.1	0.04 (0.03 - 0.05)	Observed significantly < expected
Male 70 to 79 UK	28	1219.14	3223317	73	3012.54	0.02 (0.02 - 0.03)	Observed significantly < expected
Male over 80 UK	28	1844.15	1042292	10	1473.54	0.01 (0 - 0.01)	Observed significantly < expected
Female 18 to 29 UK	42	79.84	1339334	20	122.96	0.16 (0.1 - 0.25)	Observed significantly < expected
Female 30 to 39 UK	42	197.4	2096348	48	475.86	0.1 (0.07 - 0.13)	Observed significantly < expected
Female 40 to 49 UK	42	298.24	4974220	123	1705.92	0.07 (0.06 - 0.09)	Observed significantly < expected
Female 50 to 59 UK	42	355.51	6319086	121	2583.3	0.05 (0.04 - 0.06)	Observed significantly < expected
Female 60 to 69 UK	42	503.82	4859019	110	2815.09	0.04 (0.03 - 0.05)	Observed significantly < expected
Female 70 to 79 UK	42	1143.08	3562147	75	4682.27	0.02 (0.01 - 0.02)	Observed significantly < expected
Female over 80 UK	42	1731.85	1721795	35	3428.94	0.01 (0.01 - 0.01)	Observed significantly < expected
Male 18 to 29 UK	42	49.13	986375	6	55	0.11 (0.04 - 0.23)	Observed significantly < expected
Male 30 to 39 UK	42	130.28	1582807	27	237.12	0.11 (0.08 - 0.17)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 40 to 49 UK	42	253.77	5220928	80	1523.55	0.05 (0.04 - 0.07)	Observed significantly < expected
Male 50 to 59 UK	42	472.47	6957211	138	3779.87	0.04 (0.03 - 0.04)	Observed significantly < expected
Male 60 to 69 UK	42	705.7	4966917	118	4030.65	0.03 (0.02 - 0.04)	Observed significantly < expected
Male 70 to 79 UK	42	1219.14	3223317	85	4518.82	0.02 (0.02 - 0.02)	Observed significantly < expected
Male over 80 UK	42	1844.15	1042292	12	2210.31	0.01 (0 - 0.01)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	14	79.84	1339334	18	40.99	0.44 (0.26 - 0.69)	Observed significantly < expected
0.02 (0.02 - 0.02)	14	197.4	2096348	41	158.62	0.26 (0.19 - 0.35)	Observed significantly < expected
Female 40 to 49 UK with Unk TTO	14	298.24	4974220	97	568.64	0.17 (0.14 - 0.21)	Observed significantly < expected
Female 50 to 59 UK with Unk TTO	14	355.51	6319086	90	861.1	0.01 (0.08 - 0.13)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	14	503.82	4859019	85	938.36	0.09 (0.07 - 0.11)	Observed significantly < expected
Female 70 to 79 UK with Unk TTO	14	1143.08	3562147	63	1560.76	0.04 (0.03 - 0.05)	Observed significantly < expected
Female over 80 UK with Unk TTO	14	1731.85	1721795	24	1142.98	0.02 (0.01 - 0.03)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18 to 29 UK with Unk TTO	14	49.13	986375	5	18.58	0.27 (0.09 - 0.63)	Observed significantly < expected
Male 30 to 39 UK with Unk TTO	14	130.28	1582807	23	79.04	0.29 (0.18 - 0.44)	Observed significantly < expected
Male 40 to 49 UK with Unk TTO	14	253.77	5220928	63	507.85	0.12 (0.1 - 0.16)	Observed significantly < expected
Male 50 to 59 UK with Unk TTO	14	472.47	6957211	101	1259.96	0.08 (0.07 - 0.1)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	14	705.7	4966917	96	1343.55	0.07 (0.06 - 0.09)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	14	1219.14	3223317	59	1506.27	0.04 (0.03 - 0.05)	Observed significantly < expected
Male over 80 UK with Unk TTO	14	1844.15	1042292	12	736.77	0.02 (0.01 - 0.03)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	28	79.84	1339334	20	81.98	0.24 (0.15 - 0.38)	Observed significantly < expected
Female 30 to 39 UK with Unk TTO	28	197.4	2096348	47	317.24	0.15 (0.11 - 0.2)	Observed significantly < expected
Female 40 to 49 UK with Unk TTO	28	298.24	4974220	124	1137.28	0.11 (0.09 - 0.13)	Observed significantly < expected
Female 50 to 59 UK with Unk TTO	28	355.51	6319086	123	1722.2	0.07 (0.06 - 0.09)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	28	503.82	4859019	108	1876.73	0.06 (0.05 - 0.07)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 70 to 79 UK with Unk TTO	28	1143.08	3562147	77	3121.51	0.02 (0.02 - 0.03)	Observed significantly < expected
Female over 80 UK with Unk TTO	28	1731.85	1721795	36	2285.96	0.02 (0.01 - 0.02)	Observed significantly < expected
Male 18 to 29 UK with Unk TTO	28	49.13	986375	6	37.15	0.16 (0.06 - 0.35)	Observed significantly < expected
Male 30 to 39 UK with Unk TTO	28	130.28	1582807	31	158.08	0.2 (0.13 - 0.28)	Observed significantly < expected
Male 40 to 49 UK with Unk TTO	28	253.77	5220928	83	1015.7	0.08 (0.07 - 0.1)	Observed significantly < expected
Male 50 to 59 UK with Unk TTO	28	472.47	6957211	133	2519.92	0.05 (0.04 - 0.06)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	28	705.7	4966917	117	2687.1	0.04 (0.04 - 0.05)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	28	1219.14	3223317	83	3012.54	0.03 (0.02 - 0.03)	Observed significantly < expected
Male over 80 UK with Unk TTO	28	1844.15	1042292	15	1473.54	0.01 (0.01 - 0.02)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	42	79.84	1339334	21	122.96	0.17 (0.11 - 0.26)	Observed significantly < expected
Female 30 to 39 UK with Unk TTO	42	197.4	2096348	51	475.86	0.11 (0.08 - 0.14)	Observed significantly < expected
Female 40 to 49 UK with Unk TTO	42	298.24	4974220	135	1705.92	0.08 (0.07 - 0.09)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 50 to 59 UK with Unk TTO	42	355.51	6319086	132	2583.3	0.05 (0.04 - 0.06)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	42	503.82	4859019	122	2815.09	0.04 (0.04 - 0.05)	Observed significantly < expected
Female 70 to 79 UK with Unk TTO	42	1143.08	3562147	87	4682.27	0.02 (0.01 - 0.02)	Observed significantly < expected
Female over 80 UK with Unk TTO	42	1731.85	1721795	39	3428.94	0.01 (0.01 - 0.02)	Observed significantly < expected
Male 18 to 29 UK with Unk TTO	42	49.13	986375	6	55.73	0.11 (0.04 - 0.23)	Observed significantly < expected
Male 30 to 39 UK with Unk TTO	42	130.28	1582807	32	237.12	0.13 (0.09 - 0.19)	Observed significantly < expected
Male 40 to 49 UK with Unk TTO	42	253.77	5220928	92	1523.55	0.06 (0.05 - 0.07)	Observed significantly < expected
Male 50 to 59 UK with Unk TTO	42	472.47	6957211	148	3779.87	0.04 (0.03 - 0.05)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	42	705.7	4966917	134	4030.65	0.03 (0.03 - 0.04)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	42	1219.14	3223317	95	4518.82	0.02 (0.02 - 0.03)	Observed significantly < expected
Male over 80 UK with Unk TTO	42	1844.15	1042292	17	2210.31	0.01 (0 - 0.01)	Observed significantly < expected
All 18-49 EEA/UK	14	172.45	27716022	595	1832.06	0.32 (0.3 - 0.35)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 18-49 EEA/UK with Unk TTO	14	172.45	27716022	661	1832.06	0.36 (0.33 - 0.39)	Observed significantly < expected
All 50-59 EEA/UK	14	410.74	19552392	453	3078.32	0.15 (0.13 - 0.16)	Observed significantly < expected
All 50-59 EEA/UK with Unk TTO	14	410.74	19552392	498	3078.32	0.16 (0.15 - 0.18)	Observed significantly < expected
All 60-69 EEA/UK	14	599.39	28510714	687	6550.35	0.1 (0.1 - 0.11)	Observed significantly < expected
All 60-69 EEA/UK with Unk TTO	14	599.39	28510714	751	6550.35	0.11 (0.11 - 0.12)	Observed significantly < expected
All 70-79 EEA/UK	14	1177.99	14795684	403	6680.72	0.06 (0.05 - 0.07)	Observed significantly < expected
All 70-79 EEA/UK with Unk TTO	14	1177.99	14795684	436	6680.72	0.07 (0.06 - 0.07)	Observed significantly < expected
All over 80 EEA/UK	14	1778.15	3858135	98	2629.62	0.04 (0.03 - 0.05)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	14	1778.15	3858135	117	2629.62	0.04 (0.04 - 0.05)	Observed significantly < expected
All 18-49 EEA/UK	28	172.45	27716022	747	3664.13	0.2 (0.19 - 0.22)	Observed significantly < expected
All 18-49 EEA/UK with Unk TTO	28	172.45	27716022	813	3664.13	0.22 (0.21 – 0.24)	Observed significantly < expected
All 50-59 EEA/UK	28	410.74	19552392	603	6156.64	0.1 (0.09 - 0.11)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 50-59 EEA/UK with Unk TTO	28	410.74	19552392	648	6156.64	0.11 (0.1 - 0.11)	Observed significantly < expected
All 60-69 EEA/UK	28	599.39	28510714	879	13100.69	0.07 (0.06 - 0.07)	Observed significantly < expected
All 60-69 EEA/UK with Unk TTO	28	599.39	28510714	943	13100.69	0.07 (0.07 - 0.08)	Observed significantly < expected
All 70-79 EEA/UK	28	1177.99	14795684	557	13361.44	0.04 (0.04 - 0.05)	Observed significantly < expected
All 70-79 EEA/UK with Unk TTO	28	1177.99	14795684	590	13361.44	0.04 (0.04 - 0.05)	Observed significantly < expected
All over 80 EEA/UK	28	1778.15	3858135	130	5259.23	0.02 (0.02 - 0.03)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	28	1778.15	3818955	149	5259.23	0.03 (0.02 - 0.03)	Observed significantly < expected
All 18-49 EEA/UK	42	172.45	27716022	819	5496.19	0.15 (0.14 - 0.16)	Observed significantly < expected
All 18-49 EEA/UK with Unk TTO	42	172.45	27716022	885	5496.19	0.16 (0.15 - 0.17)	Observed significantly < expected
All 50-59 EEA/UK	42	410.74	19552392	663	9234.96	0.07 (0.07 - 0.08)	Observed significantly < expected
All 50-59 EEA/UK with Unk TTO	42	410.74	19552392	708	9234.96	0.08 (0.07 - 0.08)	Observed significantly < expected
All 60-69 EEA/UK	42	599.39	28510714	988	19651.04	0.05 (0.05 - 0.05)	Observed significantly < expected

Table 41 Observed versus expected analyses for DVT without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 60-69 EEA/UK with Unk TTO	42	599.39	28510714	1052	19651.04	0.05 (0.05 - 0.06)	Observed significantly < expected
All 70-79 EEA/UK	42	117.99	14795684	620	20042.17	0.03 (0.03 - 0.03)	Observed significantly < expected
All 70-79 EEA/UK with Unk TTO	42	117.99	14795684	653	20042.17	0.03 (0.03 - 0.04)	Observed significantly < expected
All over 80 EEA/UK	42	1778.15	3858135	141	7888.85	0.02 (0.02 - 0.02)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	42	1778.15	3858135	160	7888.85	0.02 (0.02 - 0.02)	Observed significantly < expected

[a] IBM Market Scan CCAE/MDCR 2008 thru 2020Q1

Exposure until 28 December 2021

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset

Literature

A review of the literature since the time of the previous review in the 8th SSR (Review period: 01 October 2021 – 30 November 2021) through 28 December did not identify any articles discussing a possible mechanism of action between DVT with COVID-19 VACCINE ASTRAZENECA.

Summary

A total of 5407 cases of DVT without thrombocytopenia have been received for COVID-19 VACCINE ASTRAZENECA and were reviewed as part of this cumulative update. Of these 5407, there were 254 (4.7%) case reports in individuals who have received 2 doses of vaccine and the event occurred post 2nd dose and 1 case report where the individual received 3 doses, and the event occurred after 3rd dose. Nine fatal cases (9.7%) out of all 93 fatal cases (in all age groups) occurred in 18-49 age group. For all cases, there were 53 (57.0%) fatal reports in females and 40 (43.0%) fatal reports in males. There were 4816 (89.1%) serious and 591 (10.9%) non-serious case reports. The time to onset for all cases from the administration of

vaccine to the onset of a DVT event was within 28 days in 81.5% of case reports were TTO was reported. Underlying cause/confounding factors were noted in 44.8% of the 5407 cases.

Risk/confounding factors included medical histories of the following: thrombosis/embolism, hypertension, type 2 diabetes mellitus, obesity, smoking, alcoholism, varicose vein, suspected covid-19, covid-19, infections, thyroid disorders, hypercholesterolemia/dyslipidemia, peripheral venous diseases, arteriosclerosis, cancers, Factor V Leiden mutation, cardiac disorders, renal disorders, respiratory system disorders, liver disorders, gout, pregnancy, autoimmune diseases, immunodeficiency, trauma, surgeries, arthroplasties, musculoskeletal disorders, sleep disorders, cerebrovascular accident, steroid therapy, and chemotherapy.

There were no imbalances in rates of DVT between active vaccine and control group within the clinical trials for AZD1222.

The results of the observed versus expected analyses concluded that the observed cases of DVT without thrombocytopenia were significantly less than expected in the background population overall and across the different sexes, age groups, and regions.

No mechanism of action have been identified.

Conclusion

Information from this updated cumulative review did not find evidence of a new or emerging signal regarding DVT without thrombocytopenia and COVID-19 VACCINE ASTRAZENECA. No changes to the CDS or RMP are recommended. DVT without thrombocytopenia will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

15.2.9 Hearing loss

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

The MAH should continue the closely monitor hearing loss and provide a refined analysis of medically confirmed cases in the next PSUR which must include: time to onset (including median TTO after 1st or 2nd dose), duration of the symptoms, seriousness criteria, detailed description of the cases including medical history and causality assessment. Additionally the MAH is requested to present data from clinical studies, and medical literature including plausible mechanism of action. Moreover, the MAH should identify the main reported PTs and re-evaluate the feasibility of conducting O/E analysis on those specific events.

AstraZeneca's response to this request is provided below.

Review of Cases

Using the MedDRA High Level Term (HLT) Hearing loss the AstraZeneca global safety database was searched through 28 December 2021 to identify reports of hearing loss with COVID 19 VACCINE ASTRAZENECA from the post-marketing setting.

Cumulative Review (through 28 December 2021)

The search of the AstraZeneca global safety database identified a cumulative total of 1497 case reports involving 1611 events of hearing loss with COVID-19 VACCINE ASTRAZENECA through 28 December 2021.

Of the 1497 cases of hearing loss, 921 (61.5%) of were reported in females, 528 (35.3%) in males, and 48 (3.2%) of unknown gender. Age ranged from 18 years to 64 years in 1017 (67.9%) cases, ≥65 years in 317 (21.2%) cases, and 163 (10.9%) cases of unknown age. The majority of reports (1263; 84.4%) were not medically confirmed with the remaining 234 (15.6%) cases being medically confirmed.

Of these 1497 cases of hearing loss, 1178 (78.7%) were considered serious due to Death (4), Life threatening (21), Hospitalisation (115), Disability (304), and Medically important (734). There were two fatal events of hearing loss (described in the interval summary). Of the remaining 1609 events, outcomes were: Not recovered (861), Recovered (238), Recovered with sequelae (54), Recovering (228), and Unknown (228).

There were 1544 (95.8%) events that occurred after the first dose and 67 (4.2%) events that occurred after the second dose. Time to onset of events after the first dose was within one day of vaccination for 387 (25.1%) events, 2-5 days for 253 (16.4%) events, 6-10 days for 120 (7.8%) events, and 318 (20.6%) events occurred >10 days after vaccination with the first dose. Median TTO was 3 days. TTO was unknown for 466 (30.2%) events that occurred after receiving the first dose. TTO of events after the second dose was within one day of vaccination for 14 (20.9%) events, 2-5 days for 13 (19.4%) events, 6-10 days for 10 (14.9%) events, and 30 (44.8%) events occurred >10 days after vaccination with the second dose. Median TTO was 6 days. TTO was unknown for 8 (11.9%) events that occurred after receiving the second dose.

Interval Review

For the interval period (29 June 2021 – 28 December 2021) the search of the AstraZeneca global safety database identified an interval total of 690 case reports involving 745 events of hearing loss with COVID 19 VACCINE ASTRAZENECA.

Of the 690 cases of hearing loss identified in the interval search, 429 (62.2%) of were reported in females, 240 (34.8%) in males, and 21 (3.0%) of unknown gender. Age ranged from 18 years to 64 years in 470 (68.1%) cases, ≥65 years in 148 (21.4%) cases, and 72 (10.4%) cases of unknown age. The majority of reports (563; 81.6%) were not medically confirmed.

Of these 690 cases of hearing loss, 519 (75.2%) were considered serious due to Death (3), Life threatening (13), Hospitalisation (76), Disability (155), and Medically important (272). There were two fatal events of hearing loss (described below). Of the remaining 743 events, outcomes were: Not recovered (405), Recovered (97), Recovered with sequelae (38), Recovering (95), and Unknown (108).

Fatal Events of Hearing Loss

- PPD: A spontaneous report from MHRA concerning a PPD-year-old PPD with medial history of PPD received the COVID-19 VACCINE ASTRAZENECA on PPD. Nine days later, on PPD was reported to have experienced Pulmonary embolism, Lower respiratory tract infection, Chest pain, Sinus tachycardia, and Dyspnoea. On PPD was reported to have experienced Circulatory collapse, Hypotension, Metabolic acidosis, Cardiac arrest, Hypokalaemia, Hypoglycaemia, and Hyperlactacidaemia. On PPD was reported to have experienced Cardiac failure acute. On an unknown dates, PPD reportedly experienced Disseminated intravascular coagulation, Deep vein thrombosis, Seizure, Thrombocytopenia, Acute chest syndrome, Pulmonary hypertension, PPD, Haemoglobin decreased, Malaise, and Hyperhidrosis. The vaccinee reportedly died on PPD PPD. An autopsy was performed. The cause of death was reported as pulmonary embolism, acute cardiovascular failure (confirmed at autopsy), pulmonary thromboembolism, deep vein thrombosis, hypotension, heel pain, afebrile, metabolic acidosis, thrombosis, thrombocytopenia, acute chest syndrome, chest infection, sickle cell disease, pulmonary artery hypertension, PPD hearing loss, haemoglobin decreased, chest pain, cardiac arrest, unwell, sweating, sinus tachycardia, shortness of breath, crepitations, hypokalemia, hypoglycemia, hyperlactatemia, circulatory collapse and disseminated intravascular coagulation. This case is confounded by patient's medical history of PPD hearing loss.
- PPD: A spontaneous report from the regulatory authority in PPD, concerning a PPD of unknown age. On an unknown date, PPD received COVID-19 VACCINE ASTRAZENECA. On an unknown date, PPD was reported to have suffered with PPD. PPD, the vaccinee was reported to have died from the event PPD. It was not known whether an autopsy was performed. The cause of death was reported as PPD. Limited information available in this case prevents additional assessment.

There were 698 events that occurred after the first dose and 47 events that occurred after the second dose. Time to onset of events after the first dose was within one day of vaccination for 149 (21.3%) events, 2-5 days for 98 (14.0%) events, 6-10 days for 54 (7.7%) events, and 186

(26.6%) events occurred >10 days after vaccination with the first dose. Median TTO was 5 days. TTO was unknown for 211 (30.2%) events that occurred after receiving the first dose. TTO of events after the second dose was within one day of vaccination for 8 (17.0%) events, 2-5 days for 9 (19.1%) events, 6-10 days for 7 (14.9%) events, and 18 (38.3%) events occurred >10 days after vaccination with the second dose. Median TTO was 7 days. TTO was unknown for 5 (10.6%) events that occurred after receiving the second dose.

A review of medically confirmed cases of hearing loss was provided in the previous PBRER. There were 127 medically confirmed cases involving 135 events of hearing loss during the reporting period. A tabular summary of the 127 medically confirmed cases is included in Appendix 19. This Appendix includes information on time to onset (including median TTO after 1st or 2nd dose), duration of the symptoms, seriousness criteria, detailed description of the cases including medical history and causality assessment. Of these 127 cases, 99 were reported as serious due to: Death [2], Life threatening [5], Hospitalisation [9], Disability [36], Medically important [47]. The most frequently reported PTs in these 99 serious reports of hearing loss were: Hypoacusis (50), Deafness (28), and Sudden hearing loss (24). Of the 135 events, 125 were reported to have occurred after the first dose and 10 were reported to have occurred after the second dose. Median reported TTO to hearing loss events after the first dose was 4 days and median TTO to hearing loss events after the second dose was 20 days. Reported duration of symptoms was available for 32 events with a range of 0 to 55 days after vaccination (median: 0 days). Of these 127 cases, medical history was available for 45 and included: Lung disorder, COVID-19, Asthma, Fibromyalgia, Immunodeficiency, Ophthalmic migraine, Hypertension, Hearing aid user, Deafness, Malignancy, Pulmonary embolism, Facial paralysis, Atrial fibrillation, Autoimmune thyroiditis, Hypothyroidism, Asthma, Acoustic neuroma, Depression, Myocardial ischaemia, Head injury, Dyslipidaemia, Type 2 diabetes mellitus, Coronary artery disease, Auditory disorder, Chronic obstructive pulmonary disease, Sickle cell disease, Epilepsy, Deafness neurosensory, Rheumatic disorder, Deep vein thrombosis, Tinnitus, and Bronchitis chronic. The review of the 127 medically confirmed cases of Hearing loss during the interval period did not suggest a causal association between COVID-19 VACCINE ASTRAZENECA and Hearing loss.

Observed cases were significantly less than expected for all cases globally, and for all age/gender stratifications.

Observed vs. Expected

Observed cases were significantly less than expected for all cases globally, and for all age/gender stratifications Table 42.

Table 42 Observed Versus Expected Analyses for Hearing Loss Cases

AEs	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
All cases all ages RW	28	309.86	291626957	970	69273.94	0.01 (0.01 - 0.01)	Observed significantly < expected
All cases all ages RW Unk	28	309.86	291626957	1361	69273.94	0.02 (0.02 - 0.02)	Observed significantly < expected
0 to 17 Male UK	PPD						Observed significantly < expected
18 to 49 Male UK	28	148.13	7790110	75	884.63	0.08 (0.07 - 0.11)	Observed significantly < expected
50 to 59 Male UK	28	396.82	6957211	55	2116.44	0.03 (0.02 - 0.03)	Observed significantly < expected
60 to 69 Male UK	28	682.95	4966917	26	2600.47	0.01 (0.01 - 0.01)	Observed significantly < expected
70 to 79 Male UK	28	1116.25	3223317	17	2758.3	0.01 (0 - 0.01)	Observed significantly < expected
80 plus Male UK	PPD						Observed significantly < expected
0 to 17 Female UK	28	100.15	116041	0	8.91	0 (0 - 0.41)	Observed significantly < expected
18 to 49 Female UK	28	155.56	8409902	123	1002.92	0.12 (0.1 - 0.15)	Observed significantly < expected
50 to 59 Female UK	28	357.52	6319086	71	1731.93	0.04 (0.03 - 0.05)	Observed significantly < expected
60 to 69 Female UK	28	554.28	4859019	60	2064.69	0.03 (0.02 - 0.04)	Observed significantly < expected
70 to 79 Female UK	28	827.41	3562147	19	2259.48	0.01 (0.01 - 0.01)	Observed significantly < expected

Table 42 Observed Versus Expected Analyses for Hearing Loss Cases

AEs	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
80 plus Female UK	28	1196.6	1721795	8	1579.45	0.01 (0 - 0.01)	Observed significantly < expected
0 to 17 EEAUK	PPD						Observed significantly < expected
18 to 49 EEAUK	28	151.98	27716022	353	3229.19	0.11 (0.1 - 0.12)	Observed significantly < expected
50 to 59 EEAUK	28	376.09	19552392	203	5637.26	0.04 (0.03 - 0.04)	Observed significantly < expected
60 to 69 EEAUK	28	615.27	28510714	210	13447.78	0.02 (0.01 - 0.02)	Observed significantly < expected
70 to 79 EEAUK	28	959.84	14795684	82	10887.06	0.01 (0.01 - 0.01)	Observed significantly < expected
80 plus EEAUK	28	1308.04	3858135	16	3868.79	0 (0 - 0.01)	Observed significantly < expected

AE Adverse Event, CI Confidence Interval; EEA European Economic Area, RW Risk Window, UK United Kingdom, Unk Unknown.

Literature

A cumulative literature search of the Hearing loss HLT with COVID-19 vaccines found no articles of interest, including plausible mechanism of action.

Summary

The majority of the Hearing loss cases received during the reporting period were serious consumer reports, with most cases occurring in adult females (62.2%) aged 18-64 after the first dose of COVID-19 VACCINE ASTRAZENECA. The review of the 127 medically confirmed cases of Hearing loss during the interval period did not suggest a causal association between COVID-19 VACCINE ASTRAZENECA and Hearing loss. Observed cases were significantly less than expected for all cases globally, and for all age/gender stratifications. A cumulative literature search of the Hearing loss HLT with COVID-19 vaccines found no articles of interest, including plausible mechanism of action.

Conclusion

This cumulative and interval review of hearing loss with COVID-19 VACCINE ASTRAZENECA vaccination did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern. It is AstraZeneca's opinion that no update to the CDS or RMP are needed. Hearing loss will continue to be monitored as part of AstraZeneca's routine surveillance process.

15.2.10 Hemophagocytic lymphohistiocytosis (HLH)

Request

AstraZeneca received the following request from PRAC in the AR for the 8th SSR (review period: 01 October 2021 – 30 November 2021):

"In the next PSUR, the MAH is requested to search and review cases of Hemophagocytic Lymphohistiocytosis (HLH) and to review and comment on the literature on HLH in the context of vaccination and COVID-19 vaccination, including the 4 cases from publications already identified by EMA. The MAH should then discuss the need of additional data and the plausibility of causal relationship between HLH and vaccination with Vaxzevria."

AstraZeneca's response to this request is provided below.

HLH Diagnosis

HLH diagnosis is frequently difficult because of the acute and severe setting and lack of specificity in the criteria. HLH-2004 criteria are frequently used to diagnose HLH and are validated in the pediatric population. However, for adults population, the HLH-probability calculator (HScore) is frequently used as suggested by the American Society of Hematology guidelines. HScore encompasses graded clinical and laboratory parameters, and additional criteria compared to HLH-2004 (Fardet et al 2014).

In order to confirm the diagnosis of HLH, a HLH-probability (HScore) was used. The probability of suffering from HLH is less than 1% for an HS score of ≤90 and 99% for an HScore of ≥250. The HScore was calculated for each of these cases using the available information (see Table 44).

Review of Cases

A cumulative search of the AstraZeneca global patient safety database 28 December 2021 was conducted using the following MedDRA PTs: Hemophagocytic lymphohistiocytosis (HLH) with COVID-19 VACCINE ASTRAZENECA. An additional search was performed to retrieve any cases that have at least one PT from each of the categories below, ie, cases were pulled out if they had one PT from each of the categories 1-4 reported together in the same case report:

1 Splenomegaly and/or hepatomegaly and/or hepatosplenomegaly

2 Pancytopenia and/or bicytopenia and/or cytopenia and/or full blood count decreased and/or anaemia and/or red blood cell count decreased and/or white blood cell count decreased and/or leucopenia and/or thrombocytopenia and/or platelet count decreased

3 Serum ferritin increased and/or Hyperferritinaemia

4 Hyperpyrexia and/or Pyrexia

The search identified 33 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA.

Out of the 33 cases: 4 of the cases are literature reports; 1 case is a non-interventional / post-market report; 28 cases are spontaneous reports. There were no reports from clinical studies regarding HLH.

Out of the 33 cases: All of the cases were reported as serious and 23 (69.7%) were medically confirmed. There were 6 fatal reports which are discussed below. The fatal cases were confounded by risk/confounding factors summarised below.

Out of the 33 reports, 18 (54.5%) were from the United Kingdom (UK), 4 (12.1%) were from France, 3 (9.1%) were from Australia, 2 (6.1%) were from Germany and 1 (3.0%) were each from [redacted]

There were 13 (39.4%) reports in female vaccinees and 20 (60.6%) were in male vaccinees. The age range was 36-80 years of age with a median age of 59 years.
17 (51.5%) vaccinees were in the age group of 18-<65 years
of age, 12 (36.4%) vaccinees were >65 years of age, and for 4 (12.1%) vaccinees the age was unknown.

Out of the 33 cases, 21 had the time to onset (TTO) within 20 days, 5 had a TTO beyond 20 days and in the remaining 7 cases the TTO was unknown. The median TTO was 7 days (range 0-43 days).

Summary of case with fatal outcome

There were 6 case reports identified with a fatal outcome. These cases have been summarised and presented in Table 43 below.

Table 43 Summary of cases with fatal outcome

No	Case ID/Country/Age/Gender	HLH probability (%)	WHO-UMC Assessment	Relevant medical history/Concomitant medications	Time between vaccination and death-days	Other conditions associated to the fatal outcome/An autopsy (Y/N)	Additional comment
1	PPD	0.003	Non Applicable[a]	PPD	16	The patient was reported to have died from the event of PPD disseminated intravascular coagulation and herpes simplex hepatitis on an unspecified date. It was not known whether an autopsy was performed.	The event herpes simplex hepatitis occurred twelve days after the vaccination, followed by the other events. The event of HLH could have been associated with the other reported events.
2	PPD	98.9	Possible-Confounded		2	An autopsy was not performed. The cause of death was reported as sepsis.	N/A
3	PPD	0.003	Non Applicable[a]		14	The patient was reported to have died from the event of multiple organ failure. An autopsy was not performed.	Epstein-Barr virus infection and Haemophagocytic lymphohistiocytosis could be associated with all other events.
4	PPD	96	Possible-confounded		7	The cause of death was reported as oesophageal rupture and PPD. It is not known whether an autopsy was performed.	Underlying essential thrombocytopenia and PPD cancer could be contributory risk factors, and history of bee sting anaphylaxis could be possibly confounding.

Table 43 Summary of cases with fatal outcome

No	Case ID/Country/Age/Gender	HLH probability (%)	WHO-UMC Assessment	Relevant medical history/Concomitant medications	Time between vaccination and death-days	Other conditions associated to the fatal outcome/An autopsy (Y/N)	Additional comment
5	PPD	0.0725	Non Applicable[a]	PPD	7	The patient was reported to have died from the event of PPD disseminated intravascular coagulation and herpes simplex hepatitis on an unspecified date. It was not known whether an autopsy was performed.	The event herpes simplex hepatitis occurred twelve days after the vaccination, followed by the other events. The event of HLH could have been associated with the other reported events.
6	PPD	0.068	Non Applicable[a]		16	The patient was reported to have died from the event of PPD It is not known whether an autopsy was performed.	The events could be associated with each other. Underlying medical history of hypertension and asthma could possibly be risk factors for the multiple organ dysfunction syndrome. Cytomegalovirus infection could possibly be a risk factor for the events.

EBV Epstein-Barr Virus, F Female, M Male, Y Yes, N No, N/A Not Applicable, UMC Uppsala Monitoring Centre, WHO World Health Organization.

a Non Applicable applies to cases where a diagnosis has not been established (HScore below 90 and unknown bone biopsy)

Risk/confounding factor analysis

Out of the 33 cases, where sufficient information was available for assessment, 22 were confounded for medical histories and or concomitant drugs. Cases have been summarised in Table 44.

H-Score outcome

AstraZeneca calculated the H-Score was calculated for all cases using available information. Out of the 33 cases, 27 had a H-Score <90 (ie, < 1% probability of HLH), of which 9 cases had an H-Score of 0. The mean H-Score was 64 and the median H-Score was 42. The maximum H-Score observed in these cases was 254, and the corresponding HLH probability was 99.5%. 5 of the cases had high H-Scores, however these cases were confounded with medical histories and or concomitant drugs.

Causality assessment using WHO-UMC classification and outcome

Among 33 cases, the diagnosis of HLH was confirmed for 11 cases (5 based on HLH Probability of ≥ 90%; and 6 cases with positive bone marrow biopsy). WHO-UMC classification was conducted for those 11 cases and it included the following:

• Two cases were categorized as WHO-UMC “Unassessable” by AstraZeneca due to unknown TTO. Those 2 were also confounded by Immunodeficiency, thrombocytopenia and past drug therapy of hydroxycarbamide suggesting a history of blood cancer; and medical history of anaphylaxis, neoplasm malignant, pneumonitis, bronchoscopy.

• Nine cases were categorized as WHO-UMC “Possible” by AstraZeneca: 8 were confounded and 1 had limited information. Those 8 cases were confounded by myocarditis and diabetes and concomitant medication included anakinra; rheumatoid arthritis and concomitant event of sepsis; concomitant use of broad spectrum antibiotics and diabetes; JAK2-mutation positive essential thrombocythemia, breast cancer in remission, and antibiotics; autoimmune disease (Ankylosing spondylitis) and con med (antibiotics); coronary arterial stent insertion, angina pectoris, hypertension and myocardial ischaemia; Takayasu's arteritis, and concomitant events of thrombocytopenia and vasculitis; and skin cancer (Bowens disease).

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
PPD	PPD	Not recovered	Autoimmune disorder, PPD and polypharmacy	Unknown	7	18	0.009	Autoimmune disorder. Insufficient information.	Non Applicable[a]
PPD	PPD	Died	Hypertension, asthma, CMV infection, and concomitant event of sepsis and multiple organ dysfunction syndrome	Unknown	16	50	0.068	High ferritin levels. Insufficient information.	Non Applicable[a]
PPD	PPD PPD	Not recovered	Hypertension, hypothyroidism, COPD and polypharmacy.	Unknown	26	30	0.019	Low platelet count, low fibrinogen levels. Insufficient information.	Non Applicable[a]
PPD	PPD	Died	Type 2 diabetes, Herpes simplex	Unknown	16	0	0.003	T2 diabetes	Non Applicable[a]
PPD	PPD	Not recovered	Medical history of PPD	Unknown	11	85	0.594	High ferritin levels. Biopsy confirmed MAS. Insufficient information.	Possible-confounded
PPD	PPD	Not recovered	coeliac disease	Unknown	5	0	0.003	Insufficient information.	Non Applicable[a]
PPD	PPD PPD	Not recovered	Immunodeficiency, thrombocytopenia and past drug therapy PPD suggesting a history of PPD	Unknown	Unknown	35	0.026	Immunodeficiency, bone marrow biopsy confirms haemphagocytosis, unknown fever temp. Insufficient information.	Unassessable/ Unclassifiable

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
PPD	PPD PPD	Not recovered	Anaphylaxis, neoplasm malignant, pneumonitis, bronchoscopy	Unknown	Unknown	35	0.026	Low platelet count, Bone marrow showed haemophagocytosis. Insufficient information.	Unassessable/ Unclassifiable
PPD	PPD PPD	Recovering	Bowens disease	Unknown	19	250	99	Unknown fever temp, platelets count unclear, high ferritin, splenomegaly confirmed, haemophagocytosis seen on bone marrow	Possible-confounded
PPD	PPD	Not recovered	Seropositive RA and concomitant medications of PPD for rheumatoid arthritis	Unknown	22	98	1.3	RA, high ferritin, Low platelet count, low fibrinogen levels. Insufficient information.	Non Applicable[a]
PPD	PPD	Recovering	Splenectomy, PPD axillary adenopathy, arthritis rheumatoid	Unknown	0	18	0.009	RA, Insufficient information.	Non Applicable[a]
PPD	PPD	Recovering	aortic stricture, obstructive sleep apnoea syndrome, cyst of kidney, stent placement and ischaemic heart disease	Unknown	5	0	0.003	Insufficient information.	Non Applicable[a]

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
PPD	PPD	Died	Meningitis, cyst rupture, rheumatoid arthritis, and concomitant event of sepsis	Unknown	2	241	98.9	RA, Temp 38.5, low Hb, low platelet count, high ferritin count, low fibrinogen level, high triglyceride level, hepatomegaly, splenomegaly, AST level of 78	Possible-confounded
PPD	PPD	Unknown	Unknown	Unknown	Unknown	0	0.003	Fever, and high ferritin level (number was not reported).	Non Applicable[a]
PPD	PPD	Recovering	methylprednisolone sodium succinate	Unknown	7	87	0.67	Fever, hepatomegaly, splenomegaly, and high fever.	Non Applicable[a]
PPD	PPD	Not recovered	coronary arterial stent insertion, angina pectoris, hypertension and myocardial ischaemia	Unknown	9	134	11.086	Fever, high ferritin, HLH confirmed on biopsy	Possible-confounded
PPD	PPD	Recovered	Unknown	Unknown	13	0	0.003	Insufficient information..	Non Applicable[a]
PPD	PPD	Not recovered	bronchial asthma, and Heparin-induced thrombocytopenia (PF4 AK and HIPA test positive)	Unknown	5	0	0.003	Insufficient information.	Non Applicable[a]
PPD	PPD	Not recovered	Unknown	Unknown	7	107	2.3	Fever, splenomegaly, high ferritin, and bone biopsy.	Possible-limited information

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
PPD	PPD	Recovering	diabetes mellitus, hypertension and dyslipidaemia, and COVID-19	Unknown	33	87	0.67	Insufficient information.	Non Applicable[a]
PPD	PPD	Died	EBV, Rheumatoid arthritis	Unknown	43	0	0.003	Insufficient information.	Non Applicable[a]
PPD	PPD	Not recovered	Medical history of PPD	Unknown	Unknown	0	0.003	Insufficient information.	Non Applicable[a]
PPD	PPD	Not recovered	Epstein-Barr virus infection reactivation	Unknown	21	0	0.003	Insufficient information..	Non Applicable[a]
PPD	Unk /PPD	Recovering	Broad spectrum antibiotics and diabetes	Unknown	10	254	99.5	Fever, hepatomegaly, Hb, thrombocytopenia, ferritin, LDH, triglycerides, fibrinogen, ALT, bone biopsy	Possible-confounded
PPD	Unk /PPD	Died	PPD ,	Unknown	7	220	96	Fever, Hb , thrombocytopenia, ferritin,	Possible-confounded

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
			breast cancer in remission, antibiotics					LDH, Triglycerides, Fibrinogen, and bone biopsy	
PPD	Unk /PPD	Unknown	Ankylosing spondylitis, antibiotics	Unknown	8	219	96	Fever, splenomegaly, Hb, platelet number, ferritin, LDH, triglycerides, fibrinogen, ALT, and bone biopsy.	Possible-confounded
PPD	PPD	Not recovered	Unknown	Unknown	11	87	0.672	Fever, hepatosplenomegaly	Non Applicable[a]
PPD	PPD	Unknown	Medical history of PPD	Unknown	Unknown	87	0.672	Fever, hepatosplenomegaly	Non Applicable[a]
PPD	PPD	Died	PPD for chest infection	Unknown	7	51	0.0725	PPD, Fever	Non Applicable[a]
PPD	PPD	Not recovered	Type 2 diabetes, Epstein Barr virus	Unknown	Unknown	42	0.041533903	Hemoglobulin low, T2DM, low leucocyte,	Non Applicable[a]
PPD	PPD	Not recovered	PPD, and concomitant events of thrombocytopenia and vasculitis.	Unknown	19	151	26.34720296	Fever, high ferritin, HLH confirmed on biopsy, low fibrinogen	Possible-confounded

Table 44 Characteristics of Cases of HLH Following Receipt of COVID-19 VACCINE ASTRAZENECA as Reported

Case ID/Country/	Vaccinee demographic (years/gender)	Event Outcome	Confounding factors	Previous immunisation	Event Time to Onset (days)	H Score	HLH Probability (%)	Components used to calculate HScore	WHO-UMC causality assessment
PPD	PPD PPD	Not recovered	relapsing emitting PPD	Unknown	Unknown	0	0.003	Insufficient information.	Non Applicable[a]
PPD	Unk /PPD	Unknown	PPD	Unknown	3	0	0.003	Insufficient information.	Non Applicable[a]

a Non Applicable applies to cases where a diagnosis has not been established (HScore below 90 and unknown bone biopsy).

ALT Alanine Transaminase, AST Aspartate Aminotransferase, CV Cerebrovascular, EBV Epstein-Barr Virus, Hb Heamoglobin, HLH Hemophagocytic lymphohistocyosis, LDH Lactate Dehydrogenase, PF 4 Platelet Factor-4, T2DM Type 2 Diabetes Mellitus, UMC Uppsala Monitoring Centre, Unk Unknown, UTI Urinary Tract Infection, WHO World Health Organization

Observed vs. Expected Analysis

The observed versus expected (O/E) Analysis was performed for cases of HLH from the AstraZeneca Safety database that presented with a risk window of 20 days (Table 45).

The O/E analysis is highly dependent on background incidence rates used. For the calculations of the O/E analysis, the background incidence rate used is 0.36/100,000 person years (Machaczka et al 2011).

The risk window of 20 days was derived upon review of case reports of HLH and consultation with therapy area experts from academia.

Cases with a high HScore (ie, score > 200) and cases with positive bone biopsy results and known TTO were considered for determining the number of observed cases. A total of 8 observed cases were obtained, consisting of 5 cases with high HScores (Case IDs PPD) and 3 cases with positive bone biopsy results and known TTOs (Case IDs; PPD).

Table 45 Observed versus Expected Analysis

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95%CI)	Conclusion
All	20	0.36	212094099	8	41.81	0.19 (0.08 - 0.38)	Observed significantly < expected

AE, Adverse Event; BG, background; CI Confidence Interval; O/E, Observed Versus Expected.

The observed versus expected analysis of HLH cases suggested that observed cases were significantly less than expected.

Literature

A search of medical literature databases (including Embase and InsightMeme) was conducted for HLH in association with the use of COVID 19 vaccines. The search covered the cumulative period through 28 December 2021. The below mentioned terms were searched.

- 'hemophagocytic syndrome' OR 'hemophagocytic lymphohistiocytosis'

The literature search identified a total of 11 publications, of which 8 were not pertaining to this safety topic in association with COVID-19 vaccines. The remaining 3 articles are considered relevant and subsequently discussed.

- PPD: The first article (Ai et al 2021) is a letter to the editor and described a single case report of Hemophagocytic lymphohistiocytosis following ChAdOx1 nCov-19 vaccination. A PPD-year-old PPD patient presented to the hospital on PPD with 7 days of fevers, rigors, lethargy, and night sweats. First dose of ChAdOx1 nCov-19 vaccine was administered on PPD (TTO: 19 days). There were no clinical features of thrombosis. PPD had no infectious contacts or contact with PPD 2 months prior where PPD reported there were PPD Physical examination revealed splenomegaly, however, was otherwise unremarkable. Comorbidities included PPD Concomitant medications included PPD Recent blood tests in PPD demonstrated a normal platelet count, ferritin level, and liver function tests. On presentation PPD had hyponatremia with a sodium level of 125 mmol/L, elevated LDH of 854 U/L (120–250 U/L), low platelet count of 59 × 109/ L, elevated ferritin of 8498 µg/L, normal fibrinogen of 2.3 g/L, elevated D-dimer of more than 10 mg/L (<0.5 mg/L), elevated aspartate aminotransferase of 223 U/L, and alanine aminotransferase of 121 U/L. CT chest/abdomen/pelvis demonstrated splenomegaly of 16 cm and subcentimetre para-aortic lymphadenopathy, with no focus of infection. Cytomegalovirus and Epstein-Barr virus serologies, monospot, and DNA PCR, Hepatitis B, C, and HIV serologies, Q fever (Virion) and rickettsial serologies were negative. A bone marrow biopsy demonstrated evidence of hemophagocytosis. PET scan demonstrated fluorodeoxyglucose (FDG) avidity in the spleen and bone marrow, and a 12 mm FDG-avid (SUV 3.4) aortocaval lymph node. PPD fasting triglyceride level was elevated at 2.3 mmol/L. PPD soluble CD25 was elevated at 733 U/ml (27–118 U/ml). The small CD4−/CD8− gamma-delta T cell population in PPD bone marrow is commonly seen as a reactive feature in immune dysregulation. It is unclear if PPD had a pre-existing genetic predisposition to HLH as genetic testing is pending. The symptoms were resolved with conservative management.

  AstraZeneca Comment: This report describes a case with underlying PPD and possible infections (in light of PPD), which could be trigger factors to develop HLH. Due to the temporal association of 19 days, the WHO-UMC causality of the case is Possible; however, limited information on circumstances leading to the event, status of PPD, and the lack of family history and pending genetic testing results precluded a proper assessment.

- PPD: This article (Attwell et al 2021) describes 3 patients reported with Haemophagocytic lymphohistiocytosis after vaccination with VAXZEVRIA.

PPD is a PPD in PPD admitted to the hospital 10 days after receiving the first dose of ChAdOx1 nCov-19 vaccine. PPD presented with breathlessness, fever, and myalgia, with onset of symptoms 5 days postvaccination (TTO: 5 days). Comorbidities included PPD. No information was provided with regard to concomitant medications and physical examination. The patient underwent computed tomography (CT) pulmonary angiography, which showed bilateral pleural effusion. The patient had a repeat transthoracic echocardiogram which showed PPD. The patient was initially treated with broad spectrum antibiotics for infection (unspecified) and later PPD

PPD is a case of a PPD in PPD who spontaneously developed a ruptured oesophagus and died. The patent initially presented with night sweats, breathlessness, and myalgia 7 days after receiving the first dose of ChAdOx1 nCov-19 vaccine (TTO: 7 days). Comorbidities included PPD A CT scan showed PPD was admitted to the hospital, given intravenous antibiotics, and later discharged. PPD was readmitted with progressive fever, breathlessness, cough, weight loss, and general malaise, and was PPD received treatment in PPD but died due to ruptured oesophagus.

PPD is a PPD in PPD who presented with fever, diarrhoea, sore throat, and pruritic rash 8 days after receiving the first dose of ChAdOx1 nCov-19 vaccine (TTO: 8 days). Comorbidities include PPD A CT scan showed pleural effusions and a pericardial effusion. A positron emission tomography (PET) CT scan showed intense bone marrow uptake and hypersplenism. The patient was given antibiotic therapy.

The article states that all 3 patients were treated with high-dose methylprednisolone. Additionally, all 3 patients presented with elevated inflammatory markers, with subsequent evidence of HLH highlighted by elevated ferritin, cytopaenias, hypofibrinogenaemia, hypertriglyceridaemia, elevated liver enzymes, and high levels of soluble CD25. Other secondary causes of HLH were excluded by cross-sectional imaging, extensive negative infection screening including serial COVID-19 testing and negative autoimmune panels.

AstraZeneca Comment: All the 3 patients described in this article have either underlying autoinflammatory or autoimmune disease, which could be one of the triggers of developing HLH. Due to the temporal association of 10, 7 and 8 days (respectively), the WHO-UMC causality of the case is Possible; however, there is limited information on

the circumstances leading to the events, concomitant medication, and genetic testing of the patients that preluded a proper assessment of these cases.

The third article (Tang et al 2021) is a letter to the editor and described the case of a PPD -year-old PPD who developed malaise, vomiting, and persistent high fever (up to 39.7°C) shortly after receiving the first dose of the inactivated SARS-CoV-2 vaccine (TTO: 1 day). The initial evaluation showed pancytopenia, elevated triglyceride, and decreased fibrinogen. Further tests showed high serum ferritin levels (8140.4 µg/L), low NK cell cytotoxicity (50.13% to 60.83%), and positive tests for Epstein–Barr virus (EBV) DNA. Hemophagocytosis was observed in the bone marrow. Therefore, HLH was confirmed, and PPD was immediately prescribed without PPD . Signs and abnormal laboratory results resolved gradually, and the patient was discharged. The 28 known HLH-related genes were analysed by next-generation sequencing, which did not reveal a disease-causing mutation. Additionally, this patient had no remarkable medical history, symptoms of acute infection, PPD CT scan, detectable autoimmune antibodies, and recent medication intake. Moreover, although both the intracellular and extracellular EBV-DNA were positive, the serological tests (EB-VCA IgA−, EB-VCA IgM−, EB-VCA IgG+, EB-VEA IgA−, EB-VEA IgG−, EB-VNA IgG+) indicated that the infection was not a recent event. The authors concluded that, in this case, HLH was induced by the COVID-19 vaccination immuno-stimulation on a chronic EBV infection background.

AstraZeneca Comment: This article indicates active EBV infection, which could be a trigger for HLH. However, limited information on medical history and concomitant medication precluded a proper assessment. The brand name for the vaccine was not mentioned in the article and the vaccine received was reportedly inactivated. Since there is no marketing authorisation for COVID-19 VACCINE ASTRAZENECA in China it is unlikely the vaccine mentioned in this article was COVID-19 VACCINE ASTRAZENECA

Two articles discussing HLH following vaccination with COVID-19 VACCINE ASTRAZENCA were identified by PRAC in the Assessment Report for the 8th Safety Summary Report (review period: 01 October 2021 – 30 November 2021). These two articles are discussed below:

Cory et al 2021 (PPD) described a PPD -year old PPD patient who presented to the hospital 9 days after receiving PPD first dose of COVID-19 VACCINE ASTRAZENECA with fever, myalgia and sore throat. No substantial underlying medical conditions were reported. The patient was started on PPD for treatment of suspected sepsis due to infection of uncertain aetiology. Five days later, PPD developed pleuritic pain and pericardial rub. ECG and MRI showed PPD . CT identified PPD .

Blood tests showed raised inflammatory markers, low platelets and hyperferritinaemia. Given the clinical presentation in the absence of evidence of infection or malignancy, a presumptive diagnosis of HLH (H-Score 70-80%) was made. The patient was treated with PPD PPD in improvement of symptoms. However, 6 days into treatment, fever returned, and PPD developed thrombocytopenia (platelets: 70 x 109/L). Following a 5 day course of PPD , fever reportedly resolved and myalgia and chest pain were improving. PPD was discharged to home after 33 days with a weaning course of PPD .

AstraZeneca Comment: Considering the H-Score probability below 90%, lack of cytopenia or reactive bone marrow biopsy, the HLH diagnosis could not be confirmed. AstraZeneca did not assess WHO-UMC causality due to the fact that HLH diagnosis was not established. Additionally, this case is confounded by the concomitant use of antibiotics. This case is not included in Table 44 as it was received after the data-lock point of this PSUR.

Baek et al 2022 (PPD) described a PPD -year old PPD who presented to the hospital with high fever and bilateral axillar palpable masses 1 week after first vaccination with COVID-19 VACCINE ASTRAZENECA. Other reported symptoms included: hypotension, tachycardia, PPD and severe motor weakness. The patient reportedly had a medical history of PPD , but no other underlying health conditions. Medical examination by the hospital identified neutropenia, thrombocytopenia, increased ferritin, bilateral enlarged lymph nodes, and splenomegaly. Given the clinical presentation of PPD in the absence of other infectious or malignant aetiologies, the patient was diagnosed with HLH (H-Score >90%) and treated with PPD was started at an unknown period of time due to PPD . Eight weeks after HLH diagnosis, the patient was able to ambulate and was discharged from the hospital with a weaning course of steroid treatment.

AstraZeneca Comment: Considering the H-Score >90% and the 7-day time to onset after vaccination with COVID-19 VACCINE ASTRAZENECA, AstraZeneca has confirmed the diagnosis of HLH and assessed WHO-UMC causality as Possible. However, the case is confounded by the patient's age (PPD years), underlying hypertension, previous Epstein-Barr Virus (EBV VCA and EBNA IgG positive) and concurrent event of PPD This case is not included in Table 44 as it was received after the data-lock point of this PSUR.

Pre-Clinical Data

There is no relevant pre-clinical information regarding HLH.

Clinical Study Data

There were no HLH cases in the clinical study program

Mechanism of Action

The pathophysiology of acquired HLH has not yet been completely elucidated and is likely multifactorial. Studies conducted in adult patients with HLH have shown the presence of a single mutated allele of some genes affected in F-HLH, which do not fully impair the function of affected proteins. It has been suggested that acquired HLH could be the result of the combination of inherited genetic mutations and extrinsic triggers like infection, neoplasm, or autoimmunity. Overproduction of proinflammatory cytokines is observed in acquired HLH. The mechanism underlying this hypercytokinemia is poorly understood, but results from disruption to immune homeostasis, with aberrant activation of T cells, natural killer cells and macrophages leading to overproduction of inflammatory cytokines such as tumour necrosis factor (TNF)-alpha,TNF-gamma, interleukin (IL)-1, IL-2, IL-6 and haemophagocytosis. It has been suggested that the overproduction of proinflammatory mediators may be because of the sustained toll-like receptor activation by infectious or autoimmune triggers (Ponnatt et al 2021).

There are no articles with a hypothesised mechanism for development of HLH post vaccination with COVID-19 VACCINE ASTRAZENECA.

Summary

A comprehensive, cumulative review of HLH was performed by AstraZeneca of all available additional data from sources including clinical studies, literature, and post-marketing reports.

Of the 33 cases, 17 (51.5%) vaccinees were in the age group of 18-<65 years of age and 20 (60.6%) were in male vaccinees. All cases were serious and there were 6 fatal reports (all of which had confounding risk factors).

Symptoms of secondary HLH are similar to that of F-HLH, and the former is often triggered by infections, malignancies, autoimmune/autoinflammatory diseases. A genetic testing is often required to rule out F-HLH in a suspected patient.

No new safety information was identified from the literature, and there was no relevant Pre-clinical or Clinical information regarding HLH in association with COVID-19 VACCINE ASTRAZENECA.

The cases identified from AstraZeneca Safety database and EVDAS were either confounded or had limited information that precluded a complete assessment. None of the cases reported a genetic test result to rule out familial HLH. The majority (87.8%) of the cases had a very low probability of HLH (29/33 cases had HLH probability at/below 2.3%) and the number of cases with high HLH probability (above 90.0%) was 5/33 (15%). All 5 of these cases had known risk factors including rheumatoid arthritis, broad-spectrum antibiotics, breast cancer in remission,

Bowen's disease, and ankylosing spondylitis. Overall, the most common observed risk factor was autoimmune disorders.

AstraZeneca conducted WHO-UMC causality assessments for the 11 cases for which the diagnosis of HLH was established. Nine of these cases were classified as "possible". 8 of the 11 were confounded and 1 had limited information. The remaining 2 of 11 cases were unassessable because of unknown TTO. In addition, an observed versus expected analyses was conducted, which suggested observed cases were significantly less than expected.

No mechanism of action regarding HLH and COVID-19 vaccination was identified.

Conclusion

Based on the currently available data provided in this review, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between VAXZEVRIA and HLH. No update to the core data sheet/product information is warranted. HLH is closely monitored under the AESI concept of Multisystem inflammatory syndrome in children and adults (MIS-C/A). AstraZeneca will continue to closely monitor safety information for HLH from all available sources as part of routine safety surveillance activities.

15.2.11 Menstrual Disorders

AstraZeneca received the following request from PRAC in the AR for the 8th SSR (review period: 01 October 2021 – 30 November 2021):

"Menstrual disorders: The MAH should present new data from all relevant sources since the last cumulative review, discuss these findings and need to update the product information and submit proposals as appropriate."

AstraZeneca's response to this request is provided below.

Review of Cases

An analysis of medically and non-medically confirmed cases, serious or not serious, is presented since the last cumulative review (through 31 July 2021), starting from the 01 August 2021 until data lock point of the present PSUR 28 December 2021.

To perform the above mentioned analysis, the AstraZeneca global safety database was searched using the MedDRA for events under High Level Terms (HLTs): Menstruation and uterine bleeding NEC, Menstruation with decreased bleeding, Menstruation with increased bleeding and MedDRA PTs: Vaginal haemorrhage, Uterine haemorrhage and Postmenopausal haemorrhage.

The search identified a total of 6311 case reports. Of these 6311 case reports, 18 cases were erroneously reported in males but included in analysis after re-reviewing and confirmation that

these cases were in fact reported in female patients. Out of the 6311 cases, age was reported in 5555 cases as shown in Table 46.

Table 46 Age Distribution of Vaccinees Reporting Menstrual Disorders with COVID-19 VACCINE ASTRAZENECA from 01 August 2021 through 28 December 2021 (n = 5555 reports with known age).

Age Range	Number of reports	Percentage
< 18 years	22	0.39%
< 18 years	22	0.39%
18 – 29 years	1028	18.5%
30 – 39 years	1721	30.9%
40 – 49 years	2094	37.6%
50 – 59 years	540	9.7%
60 – 69 years	124	2.2%
70 – 79 years	24	0.43%
> 80 years	2	0.03%
Total	5555	100%

Of the 6311 case reports of menstrual disorders, a total of AEs of interest were reported, which are listed in below Table 47.

Table 47 Distribution of Adverse Events Preferred terms Reported in 6311 Cases Relating to Menstrual Disorders with COVID-19 VACCINE ASTRAZENECA since 01 August 2021 through 28 December 2021

Adverse Event Preferred Term	Adverse Event count	Adverse Event serious
Heavy menstrual bleeding	1,867	760
Menstrual disorder	1,189	244
Menstruation irregular	1,127	351
Menstruation delayed	998	320
Dysmenorrhoea	642	294
Intermenstrual bleeding	520	100
Amenorrhoea	507	112
Polymenorrhoea	482	118
Vaginal haemorrhage	428	198
Postmenopausal haemorrhage	205	82
Oligomenorrhoea	182	26
Hypomenorrhoea	159	47

Adverse Event Preferred Term	Adverse Event count	Adverse Event serious
Menstrual discomfort	44	4
Premenstrual pain	41	20
Premenstrual syndrome	41	21
Uterine haemorrhage	30	19
Menometrorrhagia	26	4
Abnormal uterine bleeding	11	3
Abnormal withdrawal bleeding	11	
Anovulatory cycle	10	4
Premenstrual headache	8	2
Withdrawal bleed	5	1
Premature menarche	2	1
Premenstrual dysphoric disorder	2	
Retrograde menstruation	2	1
Bleeding anovulatory	1	
Delayed menarche	1	
Polymenorrhagia	1	
Total:	8,542	2,732

Out of the total 6311 cases, the serious cases were 2058 (32.6%) and medically confirmed cases were only 494 (7.8%). Regarding outcome of all cases: it was reported as not recovering in 3506 cases (55.6%), as recovered in 1337 cases (21.2%), reported as recovering in 719 cases (11.4%), recovered with sequelae 99 cases (1.6%), with unknown outcome in 646 cases (10.2%), and reporting a fatal outcome in 4 cases (1%). Fatal cases summaries and assessments are further included below.

Table 48 provides a distribution of time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA to the reported menstrual disorder for the 7378 events where TTO was reported. Regarding time to onset, 20% of the events had a time to onset of one day post-vaccination or within the first day right after vaccination. Time to onset from vaccine till events reported was from day 2 till day 6 post vaccination in about 7.5% of the events, more than 7 days till 15 days post vaccination for 8.5% of the events, 16 days till 30 days for 9.3% of events, 30 days till 80 days for 10% of the events, more than 80 days for 6.5% of events, and the time to onset was undefined in most of the events and cases reported in 37.2% of cases. The distribution of TTO was relatively evenly (~10%) distributed across all time intervals except for the 0 to one day interval, during which the highest number of menstrual adverse events were reported (20%).

For the most commonly reported event of PT: Heavy menstrual bleeding (1867 events), it is possible that a mechanism via thrombocytopenia is involved. The risk window used for thrombocytopenia was maximum 42 days. The time to onset for the observed events of Heavy menstrual bleeding was within 42 days for 1059 out of 1867 events.

Table 48 Time to Onset of from Vaccination with COVID-19 VACCINE ASTRAZENECA to the Menstrual Disorders reported from 01 August 2021 through 28 December 2021 (n = 7378 events).

Time to onset	# of events	%
0 till 1 day	1540	20
2 till 6 days	557	7.5
7 till 15 days	629	8.5
16 till 30 days	688	9.3
30 till 80 days	737	10
more than 80 days	480	6.5
undefined	2747	37.2
Total	7378	100.0

Note: Time To Onset was reported in more than one time in some cases therefore the difference with the total amount of cases and events.

Medically confirmed events

From the total cases, 2058 cases were reported as serious. Only 493 cases were medically confirmed among all serious and non-serious cases. Line listing on serious medically confirmed cases is presented in Appendix 15. Among the medically confirmed cases no trend was seen among the presentation of the cases. Some cases were concomitantly reporting events of thrombocytopenia, bruises, other type of haemorrhages or thrombosis and general symptoms like fatigue, pain, etc, nevertheless no trend was observed. The country reporting mostly these type of cases of menstrual disorders was the United Kingdom. There were in total 127 cases of serious and medically confirmed of amenorrhea cases. Among this set of cases no trend in the PTs or in the way of presentation of these adverse events was observed. It is important to note that among the medically confirmed cases there were also cases of amenorrhea reported.

From the medically confirmed cases 8 were reported in vaccinees with current pregnancy or current spontaneous abortion: one case corresponded to a preterm delivery, 3 cases of spontaneous abortions, one case of thrombosis in a pregnant patient with vaginal haemorrhage, and 3 cases reporting vaginal haemorrhage in pregnant vaccinees together with urinary symptoms. Pregnant cases are analysed in Section 16.3.5.1 of this PSUR.

Premenopausal period and post-menopausal period

Given the lack of case-level detail surrounding menopause status, reports with patient age <49 years were considered pre-menopausal and reports with patient age >50 were considered post-menopausal.

From the total medically confirmed cases (493) there were in total 382 cases in vaccinees with less than 50 years of age which are considered among the premenopausal period. The remaining 111 cases were reported from vaccinees who were more than 50 years of age, corresponding to the post-menopausal period.

Non-Medically Confirmed

There were in total 5818 non-medically confirmed cases of menstrual disorders, from which 1931 cases were reported as serious. Among the serious cases there were 57 cases reported in pregnant vaccinees or with a past pregnancy or current spontaneous abortion. These cases are analysed among the pregnancy section of this PSUR (Section 16.3.5.1).

From the total non- medically confirmed cases (5818) there were 4586 cases in female vaccinees with less than 50 years of age which are considered among the premenopausal period. The remaining 1232 cases were reported from vaccinees who were more than 50 years of age, corresponding to the post-menopausal period.

From the non-medically confirmed cases no trend was observed as regarding the presentation of the cases, the PTs reported neither the concomitant symptoms. Most of the cases lack of information and laboratory results.

Fatal cases reporting concomitantly any menstrual disorders:

Four cases within this updated review reported a fatal outcome, which are described below.

- PPD: A PPD years old vaccinee with chronic lymphoid leukaemia, factor VII deficiency and asthma, 14 days after vaccination experienced severe thrombocytopenia and anaemia, with concomitant white cell disorder which worsened Vaginal haemorrhage was reported which resolved in 2 days. The patient died approximately 3 months after vaccination and reported cause of death was thrombocytopenia, anaemia and vaccination site hematoma.

  AstraZeneca Comment: The cause of death reported was anaemia, thrombocytopenia and vaccination site haematoma. Underlying medical condition of chronic lymphoid leukaemia and factor VII deficiency may be contributory to the events. Time between COVID-19 VACCINE ASTRAZENECA vaccination and fatal outcome was 97 days. Due to limited information regarding relevant medical, family history, concurrent conditions (viral diseases including PPD, sepsis, heat stroke, other cancer or neoplastic diseases, hypersplenism), clinical course, etiological and diagnostic work up

(autoimmune antibody titre, blood count, clotting profile, clotting factors, fibrin products, D-dimer, PF4-antibody, bone marrow biopsy, liver function tests, full haematology workup), treatment details, further clarification of the event, concomitant medication, risk factors and lifestyle, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : A PPD years old vaccinee with a medical history of PPD received COVID-19 VACCINE ASTRAZENECA at an unknown date. At an unspecified time after vaccination, the vaccinee experienced pulmonary embolism which had a fatal outcome. Menstrual disorder was reported with no time to onset and with limited information.

  AstraZeneca Comment: Fatal event of Pulmonary Embolism and menstrual disorder are not listed in the company core data sheet of COVID-19 VACCINE ASTRAZENECA. The cause of death reported was pulmonary thromboembolism (PT: Pulmonary embolism) and menstrual disorder. Due to limited information on the circumstances leading to the events, baseline health condition before the vaccination, past and current medical history (history of heart disease, lung disease, chronic conditions), concomitant medications, relevant family history, risk factors and lifestyle (smoking history, dietary preferences, physical activity), etiological, diagnostic work up (clotting factors, coagulation panel, CT-angiogram, chest x-ray and CT-scan, full gynaecologic work up) and autopsy report, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : PPD vaccinee of PPD years of age who had being vaccinated with COVID-19 VACCINE ASTRAZENECA and 10 days later had extensive thrombosis of several organs including pancreas, liver, and portal thrombosis. The causes of death were reported as Hypoperfusion; Portal vein thrombosis; Renal vein thrombosis; Splenic vein thrombosis; Arterial thrombosis; Thrombosis; and Thrombocytopenia. TTS with Intra-abdominal thrombosis was determined as primary cause of death. In the CT scan there was an PPD Vaginal haemorrhage was also reported as part of the several PTs in this case, although there is a lack of information on this specific event neither time to onset after vaccination.

  AstraZeneca Comment: It is seen that vaccinee experienced Haematochezia, Blood urine present after 14 days of vaccine administration. Vaginal haemorrhage was reported as part of the several PTs in this case, although there is a lack of information on this specific event including time to onset after vaccination. TTS reported in this case could potentially have led to secondary vaginal haemorrhage. Due to limited information on circumstances leading to events, autopsy details, pre vaccine conditions, concomitant

medications and concurrent conditions, etiological and diagnostic work up, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : PPD vaccine of PPD years of age with medical history PPD . Concomitant medication included PPD The reporter stated that COVID-19 preceded first AZ dose by 4 weeks. Patient had been taking anticoagulants for many years without noticeable bleeding. During February 2021, the patient received one dose of COVID-19 VACCINE ASTRAZENECA. On 29 June 2021, the patient experienced low platelets. During July 2021, the patient experienced stroke. On an unknown date, the patient experienced vaginal bleeding. It was reported that the patient died from the event of stroke on 19 July 2021.

  AstraZeneca Comment: This case concerns a PPD-year-old PPD vaccinee with a fatal outcome of Cerebrovascular accident in association with COVID-19 VACCINE ASTRAZENECA. Platelet count decreased and Vaginal haemorrhage were also reported. Concomitant medication PPD might be confounding for the event of Vaginal bleeding. The age of the vaccinee could also be considered a risk factor for the event of Cerebrovascular accident. Reported past and current history of stroke, hypertension, atrial fibrillation and chronic kidney disease PPD could be considered as risk factors for the event of Cerebrovascular accident. Due to limited information on the exact circumstances leading to the events, the demographic profile of the vaccinee, exact date of dose administration, exact onset of the events of Cerebrovascular accident and Vaginal haemorrhage, or risk factors the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

After the review of fatal cases, it can be concluded that the four patients died due to other events not related to menstrual disorders. The cause of death in these four cases were assessed as: severe thrombocytopenia in a chronic leukaemia PPD patient, a case of fatal TTS, one case of pulmonary embolism and one case of a fatal cerebrovascular accident. There is insufficient evidence to relate events of menstrual disorders reported and the fatal events reported in these vaccinees.

Literature

An extensive search on Embase, Pubmed and Insight meme was completed for the period of 01 August 2021 through 28 December 2021 with the following terms: Menstrual disorders, Vaginal haemorrhage, Uterine haemorrhage and Postmenopausal Haemorrhage and COVID-19 vaccine AstraZeneca.

The search obtained 3 articles of interest among 45 articles during the period, which are summarized below.

- Male et al 2021, explains that an increase reporting of menstrual changes has being reported with all Covid-19 vaccines in general to the MHRA, which has being analysed among their yellow card monitoring. It was reported that more than 30 thousand reports of these type of events were reported to the MHRA's yellow card surveillance scheme for adverse drug reactions by 02 September 2021, across all covid-19 vaccines currently offered. Several organizations launched database studies in order to clarify this topic. This article highlights that it is important to notice that most of the reports who indicate a change in the menstrual cycle did return to normal, and that there is no evidence to believe that there is any impact on fertility, as birth rates among vaccinated and unvaccinated individuals remained similar. It was also highlighted that the MHRA did not believe that there is a causal link between these reports of menstrual disorders and COVID-19 vaccination. It is also mentioned that reports have being collected among all vaccines, mRNA covid vaccines and adenovirus vectored vaccines suggesting that if there is any increase of those events, should be mainly as an immune reaction to vaccination, rather than a reaction to a specific component of any vaccine. It was noted as well that another vaccine, papilloma virus vaccine in the past has being corelated to these type of reports, although without conclusive evidence. Further investigation will be needed to further understand any potential mechanism if any. If there is any impact, the article concludes that it appears to be short, and returns to normal in the next hormonal cycle.

- Menstrual disorders are common even after viral infections. There are some articles that point that there have being reports of menstrual changes during Covid-19 infection. An article by Li et al 2020 which was a retrospective cohort study to describe any menstrual change in COVID-19 patients, found that most vaccinees who had this complain did mainly had a reduce in the amount of menstrual blood and a dysregulation in the menstrual cycle which came back to normal after the infection. This may indicate that like with other viral infections there may be some influence on COVID-19 infection and the menstrual cycle. It was concluded that the menstruation changes of these patients might be the consequence of transient sex hormone changes caused by suppression of ovarian function that quickly resume after recovery.

- Several other articles like the one from Danesh et al 2021, point to the fact that the pandemic period itself has caused transient menstrual irregularities in women.

During the reporting period, no article was identified describing a causal relationship between menstrual disorders and COVID-19 VACCINE ASTRAZENECA.

Summary

For the reporting interval, 18.5% of reports were in 18-29 year olds, 30.9% for 30-39 years, 37.6% for 40-49 years, and 12.4% were 50 years or over. 32.6% of cases were serious, with 1% (4 cases) with a fatal outcome. After the review of fatal cases, it can be concluded that the four patients died due to other events not related to menstrual disorders. Observed versus expected analysis was not performed due to the broad nature of the events in this topic

During this updated review, a reduction in the number of cases reporting any AE related to menstrual disorders was noted. Previous cumulative review which dated until 31 July 2021, included double number of the cases (more than 12000 cases) than compared to this latest review. On the current review from the 01 August 2021 until the 28 December 2021, total amount of cases were 6311, with a highest distribution of the vaccine worldwide.

The review of cases reporting menstrual disorders, no trend was seen neither on the presentation of the symptoms or signs neither on the time to onset after vaccination.

In the literature it was highlighted that most of the reports which indicated a change in the menstrual cycle did return to normal, and that there is no evidence to believe that there is any impact on fertility, as birth rates among vaccinated and unvaccinated individuals remained similar. There are also reports of menstrual changes during Covid-19 infection itself.

During the reporting interval, 18.5% of reports were in 18-29 year olds, 30.9% for 30-39 years, 37.6% for 40-49 years, and 12.4% were 50 years or over. 32.6% of cases were serious, with 1% (4 cases) with a fatal outcome. After the review of fatal cases, it can be concluded that the four patients died due to other events not related to menstrual disorders. Observed versus expected analysis was not performed due to the broad nature of the events in this topic

Conclusion

Review of the cumulative and periodic data did not identify causal association between menstrual disorders reported to the company and COVID-19 VACCINE ASTRAZENECA. No update to the product information is required on this subject. The company will continue to closely monitor these adverse events of menstrual disorders within our surveillance and vaccine monitoring activities.

15.2.12 Multisystem inflammatory syndrome in children and adults (MIS – C/A)

Request

In PRAC's Signal AR for MIS-C/A with COVID-19 VACCINE ASTRAZENECA (reference procedure: SDA-088), the following request was received:

"The MAH should continue to closely monitor this safety issue and new cases of MIS-C/A should be reported in the MSSRs and PSURs."

AstraZeneca's response to this request is provided below.

Review of Cases

Based on available data as of 28 December 2021, a review of cases of MIS-C/A received during the reporting interval (29 June 2021 – 28 December 2021) with COVID-19 VACCINE ASTRAZENECA has been provided. The MedDRA PTs used to identify these reports included: Conjunctivitis; Conjunctivitis viral; Distributive shock; Endotoxic shock; Hypotension; Hypotensive crisis; Hypovolaemic shock; Kawasaki's disease; Multisystem inflammatory syndrome in children; Multisystem inflammatory syndrome in adults; Post procedural hypotension; Procedural hypotension; Septic shock; Systemic inflammatory response syndrome; Toxic shock syndrome.

Using the search criteria above, a total of 882 reports were identified in the AstraZeneca global safety database. However, after medical review only 5 case reports meet the MIS C/A criteria or reported as multiple inflammatory syndrome, as described below. Of these 4 cases all met MIS-A criteria. There were no cases identified, which met MIS-C criteria. Furthermore, 2 of these 6 cases met BCC level 2 for MIS-A, 1 case met BCC level 1 for MIS-A, 2 cases met BCC level 3 for MIS-A and 1 case met BCC level 4 criteria.

- PPD **:** This regulatory authority case described a PPD-year-old PPD who received COVID-19 VACCINE ASTRAZENECA and experienced a serious adverse event of the PT Systemic Inflammatory Response Syndrome (SIRS; TTO after 16 days of the first dose). The vaccinee had experienced fever, vasculitic rash, purpura, urticaria, headache, diarrhoea, elevated laboratory values (elevated c-reactive protein [CRP], erythrocyte sedimentation rate [ESR], procalcitonin, IL-6), thrombocytopenia, neutropenia, lymphopenia, leukopenia, cardiovascular disorder, sinus tachycardia (154/ min), NT-proBNP normal, and troponin increased. The events resolved a week after onset. No relevant medical history and no concomitant medications were reported. There was no laboratory confirmed SARS-CoV-2 infection.

  AstraZeneca Comment: The events resolved a week after onset. No relevant medical history and no concomitant medications were reported. There was no laboratory confirmed SARS-CoV-2 infection. The events of Purpura and vasculitis rash may be in association with the listed reported event of Thromobocytopenia. AstraZeneca has assessed this case of MIS-A as BCC Level 1 due to fever (duration unknown), >2 clinical features, 1 laboratory marker of inflammation, and >2 disease activity indicators.
- PPD **:** This is a case of reported hypotension, fibrin D dimer increased, vomiting, rash, pyrexia, headache, abdominal pain, lethargy and inflammatory marker increased in a PPD-year-old PPD patient (TTO after 1 day for hypotension and pyrexia, not reported for other events) after the first dose of the vaccine.

AstraZeneca Comment: The case is confounded by the patient's medical history of stroke, cardiac disorders, and DVT. Due to limited information on other relevant medical history (type of cardiac disorder, diabetes, chronic pulmonary diseases), concurrent conditions (polycystic kidney disease, kidney stones, infections), risk factors (smoking, alcohol or drug abuse, dehydration), etiologic and diagnostic workup (recent coagulation panel, infectious blood cultures, Electrocardiography, echocardiogram, Chest X-ray, cardiologic and pneumonologist consulting), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA. This case meets the requirements for BC level 2a MIS-A ie, fever (duration unknown), ≥2 clinical features, 1 laboratory marker of inflammation.

- PPD **;** This is a case of reported Thrombocytopenia, Thrombosis, Septic shock, Abdominal pain, Pyrexia, Headache, Nausea, Hypotension, Inflammation, Tachycardia in a PPD-year-old PPD patient, TTO 15 days after PPD first dose, for the event thrombocytopenia and not reported for the other events.

AstraZeneca Comment: The case is confounded by the patient's past medical history included PPD Due to limited information on health status before vaccination, onset date and outcome of all events, circumstances leading to the events, further treatment details, further diagnostic workup, the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA. This case meets the requirements for BC level 2b MIS-A ie, fever (duration unknown), ≥2 clinical features, 1 laboratory marker of inflammation, and 1 measure of disease activity).

- PPD **;** This case involves, systemic inflammatory response syndrome along with events, PPD , neurological symptom, hypoaesthesia, allodynia, genital dysaesthesia, urinary incontinence, hyperaesthesia, hyperreflexia, urinary retention, spinal cord disorder, dural arteriovenous fistula, dysaesthesia, muscular weakness, sensory loss, extensor plantar response, neurosarcoidosis, PPD , vitamin B12 deficiency, PPD disorder, white matter lesion, CSF protein increased, pleocytosis, CSF oligoclonal band present, systemic inflammatory response syndrome, pulmonary calcification, PPD , spinal cord injury, lymphadenopathy, influenza like illness, injection site pain in a PPD-year-old PPD patient, after the first dose of the vaccine, TTO not reported for the event systemic inflammatory response syndrome.

AstraZeneca Comment: There is no sufficient information such as temperature, heart rate, respiratory rate and other relevant laboratory data to confirm the diagnosis of MIS. Additionally, the reported events of PPD , vitamin B12 deficiency, neurosarcoidosis could be considered as confounding factors to the events. Due to limited

information on health status before vaccination, onset date and outcome of all events, circumstances leading to the events, further treatment details and further diagnostic workup, the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA. This case meets the requirements for BC level 3b MIS-A (ie, fever (duration unknown), ≥2 clinical features, 1 laboratory marker of inflammation, and 1 measure of disease activity).

AstraZeneca Comment: This case concerns a PPD-years old PPD vaccinee with reported 29 serious events in association with AZD1222, out of which lymphadenopathy is listed in company core data sheet of AZD1222. The neurological events could be in association with each other. The reported events of PPD, vitamin B12 deficiency, neuro-sarcoidosis could be considered as confounding factors to the events. Due to limited information on health status before vaccination, onset date and outcome of all events, circumstances leading to the events, further treatment details, further diagnostic work up, the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between the events and AZD1222.

- PPD **:** This report involves a patient of unknown age and gender who received COVID-19 VACCINE ASTRAZENECA and experienced systemic inflammatory response syndrome. TTO was not reported and there is no additional information provided regarding heart rate, respiratory rate and other relevant laboratory data to confirm the diagnosis of MIS.

AstraZeneca Comment: In this case, it was reported systemic inflammatory response syndrome. This case meets the requirements for BC level 4 MIS-A ie, reported as MIS but does not meet BC levels 1-3 as there was limited information on patient's demographics, health status before vaccination, date of vaccination, onset date, circumstances leading to the event, treatment provided, diagnostic workup. The evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between the event and COVID-19 VACCINE ASTRAZENECA.

Observed Versus Expected Analysis for MIS-C/A

The observed versus expected (O/E) analysis considering the 5cases meeting the Brighton Criteria for Levels 1 - 3 with different risk windows (42 and 84 days) suggested that the observed cases occurred significantly less frequently than expected for UK and EEA as discussed in Table 49. Selection of risk windows 42 and 84 days was based on the article by Vogel et al 2021, which states that "vaccine related MIS-C/A, should it exist, would follow a timeline similar to MIC-C/A after natural infection, ie., presenting within 4 – 6 weeks after vaccination for MIS – C and up to 12 weeks after vaccination in MIS-A". As all the 5 cases were reported from EEA and UK, only exposure from EEA/UK was used for the O/E analysis.

Table 49 Observed Versus Expected Analysis for MIS-C/A

Topic-Region	Observed cases	Expected cases	Risk window (in days)	Background Incidence rates/100,000 Person Years[a]	Exposure	Observed over Expected ratio (95% CI)	Conclusion
MIS-C/A-EEA/UK	5	180.42	42	1.33	117969521	0.03 (0.01 - 0.06)	Observed significantly < expected
MIS-C/A-EEA/UK	5	360.84	84	1.33	117969521	0.01 (0 - 0.03)	Observed significantly < expected
MIS-C/A-EEA/UK	5	169.57	42	1.25	117969521	0.03 (0.01 - 0.07)	Observed significantly < expected
MIS-C/A-EEA/UK	5	339.14	84	1.25	117969521	0.01 (0 - 0.03)	Observed significantly < expected

a Source: Willame et al 2021 [B] (Meta-analysis estimates using random-effect model Multisystem inflammatory syndrome -Narrow)
CI Confidence Interval, MIS-C/A Multisystem Inflammatory Syndrome in children/adults, EEA European Economic Area, UK United Kingdom

Summary

The review of above 5 case reports for multisystem inflammatory syndrome received and analysed by AstraZeneca, the patients were from the age group of 18 - <65 (adult), however the median age was 40 years old, and median time to onset for all the cases was found to be 5 days. All the 5 cases were serious, but in general they had limited information and/or were confounded by alternative aetiologies. The observed versus expected analysis of MIS-C/A showed that the observed cases occurred significantly less frequently than expected. There was too limited information in these reports to make an informed assessment of causality or conclude on the presence of confounding factors.

Conclusion

Based on the currently available information, AstraZeneca did not find evidence of a new or emerging signal for MIS C/A to suggest a need to update the COVID-19 VACCINE ASTRAZENEA CDS or RMP. product information or risk management plan. MIS C/A will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts.

15.2.13 Myocarditis and Pericarditis

Request

AstraZeneca received the following request from PRAC in the AR for the 8th SSRs (review period: 01 October 2021 – 30 November 2021):

"Myocarditis and Pericarditis: (updated request): A review of cases, an update of literature findings and an update of O/E analysis stratified by age/gender/dose and various risk windows should be presented. Additionally, the MAH should discuss possible mechanisms by which the vaccine may cause myocarditis. Based on the above, the MAH should discuss the need to update the product information and submit proposals as appropriate."

AstraZeneca's responses to these requests are provided in Subsections 15.2.13.1, 15.2.13.2 and 15.2.13.3 below.

15.2.13.1 Myocarditis

Review of Cases

A search of the global patient safety database was conducted for cumulative adverse event data (from 29 December 2020 up to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PTs under SMQ narrow Myocarditis; Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Lupus myocarditis, Myocarditis post infection in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified 593 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 593 cases, 590 cases were spontaneously reported, 1 case was from Non-interventional / Post-marketing study (D8111C00004) and 2 cases were from literature. No cases were reported from clinical trial. Out of 593 cases, 42 cases were associated with the combined events of Myocarditis and Pericarditis.

The search identified 593 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 593 cases, 590 cases were spontaneously reported, 1 case was from Non-interventional / Post-marketing study (D8111C00004) and 2 cases were from literature. No cases were reported from clinical trial. Out of 593 cases, 42 cases were associated with the combined events of Myocarditis and Pericarditis.

All 593 cases were reported as serious due to the AE being reported as medically important event (384), the AE reportedly resulted in disability (87), required hospitalization (267), was life threatening (85), and/or resulted in death (15). Out of 593 cases 182 (30.7%) were medically confirmed and 411 (69.3%) were consumer reports.

The reported outcome of adverse events (AEs) were: 15 (2.5%) Died, 247 (41.7%) Not Recovered, 67 (11.3%) Recovered, 23 (3.9%) Recovered with Sequalae, 121 (20.4%) Recovering and 120 (20.2%) Unknown.

There were 15 cases with fatal outcome (case ID: PPD), which are detailed in Table 50 below.

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
1	PPD / YES / YES	PPD	PPD / Not reported	3	1 / Dose 1	Myocarditis / Died	Cardiac arrest, Ventricular fibrillation, Bundle branch block left, Pneumonia aspiration, Brain oedema, PPD, Multi-organ failure, transthoracic echocardiogram (TTE) found evidence of severe LV failure (ejection fraction (EF) less than 20%), Elevated Troponin T and D dimer / NO	Alternative causes include underlying coagulopathy disorder (previous PPD) per Death Certificate, Bronchopneumonia; Aspiration pneumonia could be a consequence of cardiac arrest; cause of death seemed of cardiac origin, possibly related to a thrombotic coronary event or a myocardial autoimmune/inflammatory process / Alternative causal factors noted (Minimum criteria- those listed in Appendix 1 of Brighton Criteria companion guide)
2	PPD / YES / NO	Unk / Unk	Not Reported / Not Reported	60	Unk / Dose 1	Myocarditis / Died	Not reported / NO	Died 60 days post vaccination, Unknown time to onset (TTO), does not meet case definition / Limited

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
								information to make any causality assessment
3	PPD / YES / NO	PPD	PPD / Not reported	22	20 / Dose 1	Myocarditis / Died	Not reported / NO	Limited work-up information reported / Limited information to make any causality assessment
4	PPD / YES / YES	PPD	Not Reported / Not Reported	Not reported	Unk / Dose 1	Myocarditis / Died	Congestive heart failure / Unk	Limited work-up information reported / Limited information to make any causality assessment
5	PPD / YES / YES	PPD	PPD / Not reported	Not reported	Unk / Dose 1	Myocarditis / Died	Myocardial infarction, vaccine-induced immune thrombotic thrombocytopenia (VITT), severe myocarditis, intracerebral haemorrhage and cerebral edema / Unk	Risk factors included significant PPD Possible alternative cause include vaccine-induced immune thrombotic thrombocytopenia (VITT) / Limited information to make any causality assessment

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
6	PPD / YES / YES	PPD	Not Reported / Not Reported	3	2 / Dose 1	Myocarditis / Died	Renal failure, septic shock, Pericardial effusion / Unk	Risk factor PPD, Limited work-up information reported / Limited information to make any causality assessment
7	PPD / YES / YES	PPD	PPD / Not reported	5	Unk / Dose 1	Myocarditis / Died	PPD, enlargement heart, PPD (confirmed at autopsy) / YES	Alternative causality included multiple co morbidities (PPD immunocompromised state, underlying CVD). autopsy was performed. The cause of death was PPD, enlargement heart (confirmed at autopsy), PPD (confirmed at autopsy) and myocarditis / C - Alternative causal factors noted (Minimum criteria- those listed in Appendix 1 of Brighton Criteria companion guide)
8	PPD / YES / NO	PPD	PPD	Not reported	Unk / Dose 1	Myocarditis / Died	The cause of death was hanging which was confirmed at autopsy. Agitation, staring, restlessness,	PPD factors contributed to outcome of event / Limited information to make any causality assessment

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
			PPD / Not reported				PPD crying, nightmare, PPD, anger, aggression and cardiomegaly / YES	
9	PPD / YES / NO	PPD	Not Reported / Not Reported	Not reported	Unk / Dose 1	Myocarditis / Died	Found dead PPD in the autopsy noticeably many clot formations (coronary arteries, Cerebral arteries), clot vitality not certain no definite cause of death can be determined / YES	Limited work up info, Unclassifiable relation between the PPD and the event / Limited information to make any causality assessment
10	PPD / YES / YES	PPD	PPD	Not reported	30 / Dose 2	Myocarditis / Died	lymphoid infiltrated into the lung, giant cells in the lung, foreign body giant cells in the lung, enlargement heart, coronary sclerosis and acute myocardial infarction / YES	Alternative causes include underlying PPD, cardiovascular disease, hypertension (ongoing), enlargement heart, ischemic cardiomyopathy, hypothyroidism (ongoing), AV block

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
			PPD					third degree, artificial cardiac pacemaker user (ongoing), coronary sclerosis, glaucoma, renal failure, acute myocardial infarction, atrial fibrillation (ongoing) and left ventricular failure (ongoing), Limited info, limited work up info / Limited information to make any causality assessment
11	PPD / YES / NO	PPD	PPD / Not reported	12	12 / Dose 1	Myocarditis / Died	Limited information conditions associated to the death was reported / Unk	Alternative causes include heart failure (confirmed at autopsy), arteriosclerosis (confirmed at autopsy), coronary sclerosis (confirmed at autopsy), cardiac hypertrophy (confirmed at autopsy); limited work up info / Limited information to make any causality assessment

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
12	PPD / YES / NO	PPD	PPD / Not reported	Not reported	Unk / Dose 1	Myocarditis / Died	Limited information conditions associated to the death was reported / Unk	Alternative causes include infection process; Limited work-up information reported / Limited information to make any causality assessment
13	PPD / YES / NO	PPD	PPD / Not reported	3	44 / Dose 1	Myocarditis / Died	Myocarditis / Unk	Alternative causes include CAD from autopsy finding "clogged coronary artery"; disease risk factor; Limited work-up information reported / Limited information to make any causality assessment
14	PPD / YES / NO	PPD	Not Reported / Not Reported	<2	1 / Dose 1	Myocarditis / Died	Cardiac arrest, Coronary artery thrombosis/ YES - (myocarditis, thrombotic myocardial infarction)	Limited work-up information reported / Limited information to make any causality assessment
15	PPD / YES / YES	PPD	Not Reported / Not Reported	3	Unk / Dose 1	Myocarditis / Pericarditis / Died	Limited information conditions associated to the	Limited work-up information reported / Limited information to

Table 50 Summary of cases with fatal outcome for myocarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) /# Dose	Event / Outcome	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/Causality Assessment
							death was reported / Unk	make any causality assessment

AV Atrioventricular, CABG Coronary Artery Bypass Graft, EF Ejection Fraction, LV Left Ventricular.

Out of the 593 reports, 320 (54.0%) from the United Kingdom, 70 (11.8%) from Australia, 65 (11.0%) from Germany, 19 (3.2%) from France, 16 (2.7%) from Austria, 13 (2.2%) from Brazil, 10 (1.7%) from Italy, 8 (1.3%) cases each from Belgium, Ireland, Spain and Sweden, 7 (1.2%) from Greece, 6 (1.0%) from Netherlands, 3 (0.5%) cases each from Denmark and Mexico, 2 (0.3) cases each from Romania, Argentina, Iceland, Canada, Norway, Guatemala and India and 1 (0.2%) case each from [redacted]

There were 294 (49.6%) reports in male vaccinees, 281 (47.4%) were in females and the gender was not reported in 18 (3.0%) cases. The age range was 17-95 years; 3 (0.5%) vaccinees were <17 years of age, 167 (28.2%) vaccinees were between age group of 18 to 40 years, 254 (42.8%) vaccinees were between age group of 40 to 65 years, 106 (17.9%) vaccinees were ≥65 years of age and for 63 (10.6%) vaccinees the age was unknown.

The adverse event preferred terms reported as Myocarditis (590), Autoimmune myocarditis (2) and Immune-mediated myocarditis (1).

In 412 (69.5%) cases myocarditis was reported after the first dose, in 116 (19.6%) cases myocarditis was reported after the second dose, in 2 (0.3%) cases myocarditis was reported after booster dose of COVID-19 VACCINE ASTRAZENECA and for 63 (10.6%) cases dose information was unknown. Time-to-onset (TTO) was reported for 304 (51.3%) cases and was unknown for 289 (48.7%). The expected TTO for myocarditis is 2-42 days. 214 (70.4%) out of 304 reported TTO cases were within the expected risk window. These data are summarized in Table 51 below.

Table 51 Time to Onset for event Myocarditis (From First / Second Dose / Booster dose / Dose Unknown)

Time to Onset of event (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From Booster Dose)	No of Case (Dose Unknown)	%
0 days	34	3			6.2
1 days	22	2			4.0
2 days	18	4			3.7
3 days	16	2			3.0
4 days	15				2.5
5 days	10				1.7
6 days	7	2			1.5
7 days	11	3			2.4
8 days	2	1			0.5
9 days	5	1			1.0

Table 51 Time to Onset for event Myocarditis (From First / Second Dose / Booster dose / Dose Unknown)

Time to Onset of event (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From Booster Dose)	No of Case (Dose Unknown)	%
10 days	6	3			1.5
11 to 20 days	36	12			8.1
21 to 30 days	31	10			6.9
31 to 40 days	13	4			2.9
41 to 50 days	8	2			1.7
51 to 60 days	6	1			1.2
61 days and above	10	4			2.4
Unknown days (missing)	162	62	2	63	48.7

The number of cases that met the criteria for Brighton Collaboration's case definition Levels were as follows:

The Brighton collaboration (Myocarditis_Version_1.5.0_16 July 2021) of the myocarditis case definition criteria were used for the review of the data available in the case reports. Based on this approach, out of the 593 cases, 5 cases fulfilled level 1 criteria, 33 fulfilled level 2 criteria, none fulfilled level 3 criteria, 304 fulfilled level 4 criteria and 251 cases fulfilled level 5 criteria.

Brighton Collaboration Level 1

Of the 593, 5 (0.8%) case reports fulfilled Brighton collaboration level 1 criteria. To fulfil this classification histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) reports are required and be indicative of myocardial inflammation, or one or elevated myocardial biomarker (Troponin T or I) and abnormal imaging study; one or more cardiac magnetic resonance (cMRI) abnormality (Patchy edema on T2 weighted images/late gadolinium enhancement on T1 weighted images with increased enhancement ratio between myocardial skeletal muscle involving ≥1 non-ischemic regional distribution with recovery) or one or more echocardiogram abnormality (New focal or diffuse left or right ventricular function (eg decreased ejection fraction)/Segmental wall motion abnormalities/Global systolic or diastolic function depression/abnormality/Ventricular dilation/Wall thickness change/Intracavitary thrombi). These cases are summarised in Table 52 below.

Table 52 Summary of cases fulfilling Brighton collaboration level 1 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
1	PPD / YES (Medically Important) / YES	Unk / PPD	PPD	Unk / Dose 1	Myocarditis / Not recovered	Elevated troponin and Echo finding of new unexplained regional wall abnormalities and new cardiac impairment, >1 cardiac symptom (chest pain and palpitation) / Limited information to make any causality assessment
2	PPD / YES (LT and Hospitalization) / YES	PPD	PPD	Unk / Dose 1	Myocarditis / Recovered	> 1 echocardiogram (Severe global LV dysfunction and Pericardial effusion, elevated cardiac biomarker (troponin) / Limited information to make any causality assessment
3	PPD / YES (Hospitalization) / NO	PPD	PPD / Not Reported	2 / Dose 1	Myocarditis / Not recovered	Echocardiogram finding of diffuse hypokinesia with EF 40 percent and elevated troponin / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
4	PPD / YES (Medically Important)/ YES	PPD	PPD / Not Reported	26 / Dose 1	Myocarditis / Recovered	cMRI findings of Myocardial inflammation, hyperaemia and late gadolinium myocardial enhancement, elevated cardiac biomarker (troponin) / Limited information to make any causality assessment
5	PPD / YES (Hospitalization and Medically Important) / NO	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Unk	Endocardial biopsy performed and result was demonstrating acute neutrophilic myocarditis (myocardial inflammation) / Limited information to make any causality assessment

AV Atrioventricular, cMRI Cardiac Magnetic resonance imaging, EF: Ejection Fraction, F Female, LT Life threatening, LV Left Ventricular, M Male.

Brighton Collaboration Level 2

Of the 593, 33 (5.6%) case reports fulfilled Brighton collaboration level 2 criteria. 5 of the 33 cases had both Myocarditis and Pericarditis event. The cases fulfil this classification by the clinical course, examination findings and test results indicative of Myocarditis based on cardiac symptoms (Acute chest pain or pressure/Palpitations/Dyspnoea after exercise, at rest or lying down/Diaphoresis/Sudden death) or non-specific symptoms (Fatigue/Abdominal pain/Dizziness /syncope/Oedema/Cough) or non-specific symptoms in infant/young child (Irritability/Vomiting/Poor feeding/Tachypnoea/Lethargy), elevated myocardial biomarker

(Troponin T or I), Echocardiogram abnormality or Electrocardiogram abnormality that are new and/or normalize on recovery. These cases are summarised in Table 53 below.

The reports had limited information to make causality assessment or alternative causal factors were noted.

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
1	PPD / YES (LT and Hospitalization) / YES	PPD	PPD / Not Reported	0 / Dose 1	Myocarditis / Recovering	EKG finding, >1 myocardial biomarker, >1 cardiac symptoms / Limited information to make any causality assessment
2	PPD / YES (Hospitalization and Medically Important) / NO	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Unk	Chest pain with elevated Troponin. Limited information. TTO Unk./ Limited information to make any causality assessment
3	PPD / YES (Hospitalization and Medically Important) / YES	PPD	Not Reported / Not Reported	4 / Dose 1	Myocarditis / Recovering	Probable cause. EKG+, CT pericardial effusion / No reasonable alternative causal factors noted and causal association with AZD1222 cannot be ruled out (Minimum criteria for assessment- Med history and concomitant meds provided, TTO, alternative factors

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
						ruled out) / Limited information to make any causality assessment
4	PPD / YES (Hospitalization and Medically Important) / NO	PPD	Not reported / PPD	0 / Dose 1	Myocarditis / Not recovered	Cardiac symptoms + Elevated troponin / Limited information to make any causality assessment
5	PPD / YES (Hospitalization)/ NO	PPD	PPD	14 / Dose 2	Myocarditis / Not recovered	Cardiac symptoms + Increased Troponin, limited info / Limited information to make any causality assessment
6	PPD / YES(Hospitalization and Medically Important)/ YES	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Pericarditis / Not recovered / Not recovered	Cardiac symptoms + Non-specific cardiac symptoms + Troponin / Limited information to make any causality assessment
7	PPD / YES (Hospitalization and LT)/ YES	PPD	PPD / Not reported	1 / Dose 1	Myocarditis / Recovering	Chest pain / Troponin increase; limited information / Limited information to make any causality assessment
8	PPD / YES (Hospitalization	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Unk	Chest pain + Increased troponin + ECG and Echo

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
	and Medically Important) / NO					finding (widespread ST elevation; PR depression, EF 50% - low to normal) / Limited information to make any causality assessment
9	PPD / YES (Hospitalization and Medically Important) / NO	PPD	Not Reported / Not Reported	7 / Dose 1	Myocarditis / Not recovered	Chest pain + Troponin / Limited information to make any causality assessment
10	PPD / YES (Hospitalization and Medically Important) / NO	PPD	Not Reported / Not Reported	10 / Dose 1	Myocarditis / Recovering	Chest pain + Troponin increase / Limited information to make any causality assessment
11	PPD / YES (Hospitalization) / YES	PPD	PPD	14 / Dose 2	Myocarditis / Recovering	Chest pain + Troponin increased, Limited info, limited work up info/ Limited information to make any causality assessment
12	PPD / YES (Hospitalization) / YES	PPD	PPD / Not reported	14 / Dose 1	Myocarditis / Not recovered	Chest pain + increased Troponin / Limited information to make any causality assessment
13	PPD / YES (Hospitalization) / YES	PPD	PPD / Not reported	17 / Dose 1	Myocarditis / Unk	ECG findings (slight axis shift to the right. After review by a cardiologist, BRD

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
						plus BAV 1 grade ECOTT) + chest and Troponin, Limited info, limited work up info / Limited information to make any causality assessment
14	PPD / YES (Medically Important) / YES	PPD	Not Reported / Not Reported	107 / 30 / Dose 2	Myocarditis / Recovering	Chest Pain + increased Troponin + ECG result: saddle ST changes in lateral leads / Limited information to make any causality assessment
15	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	3 / Dose 1	Myocarditis / Pericarditis / Not recovered / Unk	Troponin increased + Cardiac symptom (Chest pain) + ECG findings were as follows: diffuse concave upward ST segment elevation), Limited info, limited work up info / Limited information to make any causality assessment
16	PPD / YES (Hospitalization and Medically Important) / YES	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Pericarditis / Not recovered / Unk	Cardiac symptom (tachycardia, chest pain) + Echocardiogram (ECHO) showed small pericardial effusion, Limited

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
						info, limited work up info / Limited information to make any causality assessment
17	PPD / YES (Medically Important) / NO	PPD	PPD	19 / Dose 1	Myocarditis / Recovering	Cardiac Symptom (Chest pain, tachycardia, dyspnoea) + included ECG, patient initially had sinus rhythm + cardiac biopsy coronary angiography showed mild disease in various vessels + cardiology review Atrial flutter, PPD had ablation and had remained in sinus rhythm + echo in PPD showed mild impairment right ventricle, Limited info, limited work up info/ Limited information to make any causality assessment
18	PPD / YES (Hospitalization, LT, Disability and Medically Important) / YES	Unk / PPD	PPD	16 / Dose 1	Pericarditis / Myocarditis / Recovering / Unk	Troponin level increased + cardio symptom (chest pain + dyspnoea), limited work up info / Limited information to

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
						make any causality assessment
19	PPD / YES (Hospitalization, LT, Disability and Medically Important) / YES	PPD	Not Reported / Not Reported	18 / Dose 1	Myocarditis / Recovering	Troponin T result found to be 77 nanogram per litre + Cardio symptom (dyspnoea + left ventricular hypokinesia + tachycardia) + Echocardiogram result found to be hypokinesis of septum, inferior and posterior wall, limited work up info / Limited information to make any causality assessment
20	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	7 / Dose 2	Myocarditis / Recovering	Chest pain + increased Troponin; limited work up info / Limited information to make any causality assessment
21	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	3 / Dose 1	Myocarditis / Unk	Chest discomfort + troponin raised; limited work up info / Limited information to make any causality assessment
22	PPD / YES (Medically Important)/ NO	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Unk	Chest pain + increased Troponin; limited work up info /

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
						Limited information to make any causality assessment
23	PPD / YES (Disability) / NO	PPD /	PPD / Not reported	Unk / Dose 1	Myocarditis / Unk	Chest pain + raised Troponin; Limited work up info / Limited information to make any causality assessment
24	PPD / YES (Hospitalization and Medically Important) / YES	/ PPD	Not reported / PPD	1 / Dose 1	Myocarditis / Not recovered	Chest pain + lethargy + raised Troponin; Limited work up info / Limited information to make any causality assessment
25	PPD / YES (Hospitalization and Medically Important) / NO	PPD	PPD / Not reported	14 / Dose 1	Myocarditis / Recovered	Chest pain + raised Troponin; Limited work up info / Limited information to make any causality assessment
26	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	Unk / Dose 2	Myocarditis / Recovered	Chest pain + increased Troponin; the timing of the vaccine exposure, onset of event and covid infection is not clear; limited info / Limited information to make any causality assessment

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
27	PPD / YES (LT)/ NO	PPD	Not Reported / Not reported	Unk / Dose 1	Pericarditis / Myocarditis / Unk	Chest Pain + fatigue + palpitation + Dyspnoea + increased troponin; limited info; work up info / Limited information to make any causality assessment
28	PPD / YES (Hospitalization) / YES	PPD	PPD	5 / Dose 1	Myocarditis / Recovered	Chest pain + raised troponin + ECG, showing in one of them bigeminism ventricular and in followed, ST depression accented in V3-V6, in the bottom wall and with supra-ST on the high lateral wall / Limited information to make any causality assessment
29	PPD / YES (Hospitalization and Medically Important) / YES	PPD	Not Reported / Not Reported	11 / Dose 1	Myocarditis / Recovered with sequelae	Chest pain + ejection fraction decreased + atrioventricular block complete / Limited information to make any causality assessment
30	PPD / YES	PPD	Not Reported / Not Reported	Unk / Dose 1	Myocarditis / Unk	Malaise + chest discomfort +increased

Table 53 Summary of cases fulfilling Brighton collaboration level 2 for myocarditis

Sr No	Case ID/ Country/ Case Serious -Y/N (Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
	(Medically Important)/ YES					troponin + ECG finding slight concave ST1 / Limited information to make any causality assessment
31	PPD / YES (Hospitalization and Medically Important) / YES	Unk / PPD	Not Reported / Not Reported	10 / Dose 1	Myocarditis / Not recovered	Chest pain + ejection fraction decreased + atrioventricular block complete / Limited information to make any causality assessment
32	PPD / YES (Hospitalization and Disability) / NO	PPD	Not Reported / Not Reported	10 / Dose 1	Myocarditis / Recovered with sequelae	Palpitation + Fatigue + increased Troponin / Limited information to make any causality assessment
33	PPD / YES (Hospitalization and LT) / NO	PPD	Not Reported / Not Reported	14 / Dose 1	Myocarditis / Recovered with sequelae	Chest pain + increased troponin / Limited information to make any causality assessment

AV Atrioventricular, cMRI Magnetic resonance imaging, CK Creatinine Kinase, CRP C-reactive protein, CT Computed tomography, ECG electrocardiography EKG: Electrocardiogram, EF: Ejection Fraction, LT Life threatening, TTO Time to onset; Y Yes

Brighton Collaboration Level 3

Of the 593, no case reports fulfilled Brighton collaboration level 3 criteria. To fulfil this classification there should be presence of one of the following factors: cardiac symptoms (Acute chest pain or pressure/Palpitations/Dyspnoea after exercise, at rest or lying

down/Diaphoresis/Sudden death) or non-specific symptoms (Fatigue/Abdominal pain/Dizziness /syncope/Oedema/Cough) or non-specific symptoms in infant/young child (Irritability/Vomiting/Poor feeding/Tachypnea/Lethargy), and one or more (≥1) elevated biomarker of inflammation (C-Reactive Protein OR Erythrocyte sedimentation rate OR D-Dimer) and >1 non-specific EKG abnormalities that are new and/or normalize on recovery.

Brighton Collaboration Level 4

Based on the review, 304 (51.3%) out of 593 cases were classified as Brighton collaboration level 4. These cases had insufficient evidence to meet level 3, 2 of the case definitions.

Brighton Collaboration 5

Based on the review, 251 (42.3%) out of 593 cases were classified as Brighton collaboration level 5 (ie, Myocarditis excluded due to an alternative diagnosis, hence a not a case of Myocarditis).

Generally, there was too limited information in many case reports to make an informed assessment of causality or conclude on the presence of confounding factors.

Observed vs. Expected Analysis

As requested by PRAC, an Observed versus Expected (O/E) analyses have been conducted for myocarditis cases (medically confirmed and not confirmed) received by the DLP of 28 December 2021. The expected TTO for myocarditis is 2-42 days. The data are stratified by age categories (18–49 years, 50–59 years, 60–69 years, 70–79 years, ≥ 80 years), gender, for various risk windows (7 days, 14 days, 21 days, and 42 days) and with dose details (dose 1 and dose 2 for regions EEA, United Kingdom, Argentina, Australia, Canada, Chile, Malaysia and Philippines).

O/E analyses for cases of myocarditis are shown below in Table 54. Background incidence rates from Truven Marketscan (2019) have been used for O/E analyses. These include hospitalized and non-hospitalized cases myocarditis cases.

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - All cases, all ages (RW 7) MC and NC	7	9.62	291626957	149	537.67	0.28 (0.23 - 0.33)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - All cases, all ages (RW 14) MC and NC	14	9.62	291626957	191	1075.35	0.18 (0.15 - 0.2)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 21) MC and NC	21	9.62	291626957	218	1613.02	0.14 (0.12 - 0.15)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 42) MC and NC	42	9.62	291626957	276	3226.05	0.09 (0.08 - 0.1)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 7+Unk) MC and NC	7	9.62	291626957	434	537.67	0.81 (0.73 - 0.89)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 14+Unk) MC and NC	14	9.62	291626957	476	1075.35	0.44 (0.4 - 0.48)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 21+Unk) MC and NC	21	9.62	291626957	503	1613.02	0.31 (0.29 - 0.34)	Observed significantly < expected
Myocarditis - All cases, all ages (RW 42+Unk) MC and NC	42	9.62	291626957	561	3226.05	0.17 (0.16 - 0.19)	Observed significantly < expected
Myocarditis - All ages (RW 7) MC	7	9.62	291626957	72	537.67	0.13 (0.1 - 0.17)	Observed significantly < expected
Myocarditis - All ages (RW 14) MC	14	9.62	291626957	90	1075.35	0.08 (0.07 - 0.1)	Observed significantly < expected
Myocarditis - All ages (RW 21) MC	21	9.62	291626957	102	1613.02	0.06 (0.05 - 0.08)	Observed significantly < expected
Myocarditis - All ages (RW 42) MC	42	9.62	291626957	123	3226.05	0.04 (0.03 - 0.05)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - All ages (RW 7+Unk) MC	7	9.62	291626957	119	537.67	0.22 (0.18 - 0.26)	Observed significantly < expected
Myocarditis - All ages (RW 14+Unk) MC	14	9.62	291626957	137	1075.35	0.13 (0.11 - 0.15)	Observed significantly < expected
Myocarditis - All ages (RW 21+Unk) MC	21	9.62	291626957	149	1613.02	0.09 (0.08 - 0.11)	Observed significantly < expected
Myocarditis - All ages (RW 42+Unk) MC	42	9.62	291626957	170	3226.05	0.05 (0.05 - 0.06)	Observed significantly < expected
Myocarditis 18-49 (EEA/UK) MC and NC	7	8.19	27716022	59	43.5	1.36 (1.03 - 1.75)	Observed significantly > expected
Myocarditis 50-59 (EEA/UK) MC and NC	7	9.5	19552392	22	35.6	0.62 (0.39 - 0.94)	Observed significantly < expected
Myocarditis 60-69 (EEA/UK) MC and NC	7	13.33	28510714	18	72.84	0.25 (0.15 - 0.39)	Observed significantly < expected
Myocarditis 70-79 (EEA/UK) MC and NC	7	20.03	14795684	13	56.8	0.23 (0.12 - 0.39)	Observed significantly < expected
Myocarditis ≥ 80 (EEA/UK) MC and NC	7	13.51	3858135	0	9.99	0 (0 - 0.37)	Observed significantly < expected
Myocarditis 18-49 (EEA/UK) MC and NC	14	8.19	27716022	71	87.01	0.82 (0.64 - 1.03)	Observed < expected
Myocarditis 50-59 (EEA/UK) MC and NC	14	9.5	19552392	32	71.2	0.45 (0.31 - 0.63)	Observed significantly < expected
Myocarditis 60-69 (EEA/UK) MC and NC	14	13.33	28510714	24	145.67	0.16 (0.11 - 0.25)	Observed significantly < expected
Myocarditis 70-79 (EEA/UK) MC and NC	14	20.03	14795684	17	113.6	0.15 (0.09 - 0.24)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis ≥ 80 (EEA/UK) MC and NC	14	13.51	3858135	0	19.98	0 (0 - 0.18)	Observed significantly < expected
Myocarditis 18-49 (EEA/UK) MC and NC	21	8.19	27716022	78	130.51	0.6 (0.47 - 0.75)	Observed significantly < expected
Myocarditis 50-59 (EEA/UK) MC and NC	21	9.5	19552392	33	106.8	0.31 (0.21 - 0.43)	Observed significantly < expected
Myocarditis 60-69 (EEA/UK) MC and NC	21	13.33	28510714	29	218.51	0.13 (0.09 - 0.19)	Observed significantly < expected
Myocarditis 70-79 (EEA/UK) MC and NC	21	20.03	14795684	22	170.39	0.13 (0.08 - 0.2)	Observed significantly < expected
Myocarditis ≥ 80 (EEA/UK) MC and NC	21	13.51	3858135	0	29.97	0 (0 - 0.12)	Observed significantly < expected
Myocarditis 18-49 (EEA/UK) MC and NC	42	8.19	27716022	102	261.03	0.39 (0.32 - 0.47)	Observed significantly < expected
Myocarditis 50-59 (EEA/UK) MC and NC	42	9.5	19552392	45	213.6	0.21 (0.15 - 0.28)	Observed significantly < expected
Myocarditis 60-69 (EEA/UK) MC and NC	42	13.33	28510714	38	437.02	0.09 (0.06 - 0.12)	Observed significantly < expected
Myocarditis 70-79 (EEA/UK) MC and NC	42	20.03	14795684	25	340.79	0.07 (0.05 - 0.11)	Observed significantly < expected
Myocarditis ≥ 80 (EEA/UK) MC and NC	42	13.51	3858135	0	59.94	0 (0 - 0.06)	Observed significantly < expected
Myocarditis Female 18 to 29 (UK) MC and NC	7	5.91	1339334	1	1.52	0.66 (0.02 - 3.67)	Observed < expected
Myocarditis Female 30 to 39 (UK) MC and NC	7	5.68	2096348	4	2.28	1.75 (0.48 - 4.49)	Observed > expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis Female 40 to 49 (UK) MC and NC	7	5.5	4974220	7	5.24	1.34 (0.54 - 2.75)	Observed > expected
Myocarditis Female 50 to 59 (UK) MC and NC	7	7.5	6319086	6	9.08	0.66 (0.24 - 1.44)	Observed < expected
Myocarditis Female 60 to 69 (UK) MC and NC	7	12.21	4859019	2	11.37	0.18 (0.02 - 0.64)	Observed significantly < expected
Myocarditis Female 70 to 79 (UK) MC and NC	7	18.88	3562147	4	12.89	0.31 (0.08 - 0.79)	Observed significantly < expected
Myocarditis Female 80 plus (UK) MC and NC	7	13.81	1721795	0	4.56	0 (0 - 0.81)	Observed significantly < expected
Myocarditis Male 18 to 29 (UK) MC and NC	7	11.79	986375	4	2.23	1.79 (0.49 - 4.59)	Observed > expected
Myocarditis Male 30 to 39 (UK) MC and NC	7	10.67	1582807	4	3.24	1.23 (0.34 - 3.16)	Observed > expected
Myocarditis Male 40 to 49 (UK) MC and NC	7	10.14	5220928	5	10.15	0.49 (0.16 - 1.15)	Observed < expected
Myocarditis Male 50 to 59 (UK) MC and NC	7	11.73	6957211	6	15.64	0.38 (0.14 - 0.84)	Observed significantly < expected
Myocarditis Male 60 to 69 (UK) MC and NC	7	14.57	4966917	2	13.87	0.14 (0.02 - 0.52)	Observed significantly < expected
Myocarditis Male 70 to 79 (UK) MC and NC	7	21.39	3223317	0	13.21	0 (0 - 0.28)	Observed significantly < expected
Myocarditis Male 80 plus (UK) MC and NC	7	13.09	1042292	0	2.61	0 (0 - 1.41)	Observed < expected
Myocarditis Female 18 to 29 (UK) MC and NC	14	5.91	1339334	1	3.03	0.33 (0.01 - 1.84)	Observed < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis Female 30 to 39 (UK) MC and NC	14	5.68	2096348	4	4.56	0.88 (0.24 - 2.25)	Observed < expected
Myocarditis Female 40 to 49 (UK) MC and NC	14	5.5	4974220	10	10.49	0.95 (0.46 - 1.75)	Observed < expected
Myocarditis Female 50 to 59 (UK) MC and NC	14	7.5	6319086	10	18.17	0.55 (0.26 - 1.01)	Observed < expected
Myocarditis Female 60 to 69 (UK) MC and NC	14	12.21	4859019	4	22.74	0.18 (0.05 - 0.45)	Observed significantly < expected
Myocarditis Female 70 to 79 (UK) MC and NC	14	18.88	3562147	4	25.78	0.16 (0.04 - 0.4)	Observed significantly < expected
Myocarditis Female 80 plus (UK) MC and NC	14	13.81	1721795	0	9.11	0 (0 - 0.4)	Observed significantly < expected
Myocarditis Male 18 to 29 (UK) MC and NC	14	11.79	986375	5	4.46	1.12 (0.36 - 2.62)	Observed > expected
Myocarditis Male 30 to 39 (UK) MC and NC	14	10.67	1582807	4	6.47	0.62 (0.17 - 1.58)	Observed < expected
Myocarditis Male 40 to 49 (UK) MC and NC	14	10.14	5220928	9	20.29	0.44 (0.2 - 0.84)	Observed significantly < expected
Myocarditis Male 50 to 59 (UK) MC and NC	14	11.73	6957211	8	31.28	0.26 (0.11 - 0.5)	Observed significantly < expected
Myocarditis Male 60 to 69 (UK) MC and NC	14	14.57	4966917	3	27.74	0.11 (0.02 - 0.32)	Observed significantly < expected
Myocarditis Male 70 to 79 (UK) MC and NC	14	21.39	3223317	1	26.43	0.04 (0 - 0.21)	Observed significantly < expected
Myocarditis Male 80 plus (UK) MC and NC	14	13.09	1042292	0	5.23	0 (0 - 0.71)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis Female 18 to 29 (UK) MC and NC	21	5.91	1339334	1	4.55	0.22 (0.01 - 1.22)	Observed < expected
Myocarditis Female 30 to 39 (UK) MC and NC	21	5.68	2096348	4	6.85	0.58 (0.16 - 1.5)	Observed < expected
Myocarditis Female 40 to 49 (UK) MC and NC	21	5.5	4974220	11	15.73	0.7 (0.35 - 1.25)	Observed < expected
Myocarditis Female 50 to 59 (UK) MC and NC	21	7.5	6319086	10	27.25	0.37 (0.18 - 0.67)	Observed significantly < expected
Myocarditis Female 60 to 69 (UK) MC and NC	21	12.21	4859019	6	34.11	0.18 (0.06 - 0.38)	Observed significantly < expected
Myocarditis Female 70 to 79 (UK) MC and NC	21	18.88	3562147	4	38.67	0.1 (0.03 - 0.26)	Observed significantly < expected
Myocarditis Female 80 plus (UK) MC and NC	21	13.81	1721795	0	13.67	0 (0 - 0.27)	Observed significantly < expected
Myocarditis Male 18 to 29 (UK) MC and NC	21	11.79	986375	5	6.69	0.75 (0.24 - 1.74)	Observed < expected
Myocarditis Male 30 to 39 (UK) MC and NC	21	10.67	1582807	5	9.71	0.51 (0.17 - 1.2)	Observed < expected
Myocarditis Male 40 to 49 (UK) MC and NC	21	10.14	5220928	9	30.44	0.3 (0.14 - 0.56)	Observed significantly < expected
Myocarditis Male 50 to 59 (UK) MC and NC	21	11.73	6957211	9	46.92	0.19 (0.09 - 0.36)	Observed significantly < expected
Myocarditis Male 60 to 69 (UK) MC and NC	21	14.57	4966917	3	41.61	0.07 (0.01 - 0.21)	Observed significantly < expected
Myocarditis Male 70 to 79 (UK) MC and NC	21	21.39	3223317	2	39.64	0.05 (0.01 - 0.18)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis Male 80 plus (UK) MC and NC	21	13.09	1042292	0	7.84	0 (0 - 0.47)	Observed significantly < expected
Myocarditis Female 18 to 29 (UK) MC and NC	42	5.91	1339334	2	9.1	0.22 (0.03 - 0.79)	Observed significantly < expected
Myocarditis Female 30 to 39 (UK) MC and NC	42	5.68	2096348	6	13.69	0.44 (0.16 - 0.95)	Observed significantly < expected
Myocarditis Female 40 to 49 (UK) MC and NC	42	5.5	4974220	13	31.46	0.41 (0.22 - 0.71)	Observed significantly < expected
Myocarditis Female 50 to 59 (UK) MC and NC	42	7.5	6319086	12	54.5	0.22 (0.11 - 0.38)	Observed significantly < expected
Myocarditis Female 60 to 69 (UK) MC and NC	42	12.21	4859019	6	68.22	0.09 (0.03 - 0.19)	Observed significantly < expected
Myocarditis Female 70 to 79 (UK) MC and NC	42	18.88	3562147	5	77.34	0.06 (0.02 - 0.15)	Observed significantly < expected
Myocarditis Female 80 plus (UK) MC and NC	42	13.81	1721795	0	27.34	0 (0 - 0.13)	Observed significantly < expected
Myocarditis Male 18 to 29 (UK) MC and NC	42	11.79	986375	9	13.37	0.67 (0.31 - 1.28)	Observed < expected
Myocarditis Male 30 to 39 (UK) MC and NC	42	10.67	1582807	6	19.42	0.31 (0.11 - 0.67)	Observed significantly < expected
Myocarditis Male 40 to 49 (UK) MC and NC	42	10.14	5220928	11	60.88	0.18 (0.09 - 0.32)	Observed significantly < expected
Myocarditis Male 50 to 59 (UK) MC and NC	42	11.73	6957211	12	93.84	0.13 (0.07 - 0.22)	Observed significantly < expected
Myocarditis Male 60 to 69 (UK) MC and NC	42	14.57	4966917	4	83.22	0.05 (0.01 - 0.12)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis Male 70 to 79 (UK) MC and NC	42	21.39	3223317	2	79.28	0.03 (0 - 0.09)	Observed significantly < expected
Myocarditis Male 80 plus (UK) MC and NC	42	13.09	1042292	0	15.69	0 (0 - 0.24)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 7) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	9.62	120426885	127	222.03	0.57 (0.48 - 0.68)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 7 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	9.62	120426885	276	222.03	1.24 (1.1 - 1.4)	Observed significantly > expected
Dose 2 - All cases, all ages (RW 7) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	9.62	101895308	16	187.87	0.09 (0.05 - 0.14)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 7 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	9.62	101895308	74	187.87	0.39 (0.31 - 0.49)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 14) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	9.62	120426885	154	444.06	0.35 (0.29 - 0.41)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Dose 1 - All cases, all ages (RW 14 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	9.62	120426885	303	444.06	0.68 (0.61 - 0.76)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 14) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	9.62	101895308	28	375.73	0.07 (0.05 - 0.11)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 14 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	9.62	101895308	85	375.73	0.23 (0.18 - 0.28)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 21) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	9.62	120426885	176	666.1	0.26 (0.23 - 0.31)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 21 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	9.62	120426885	325	666.1	0.49 (0.44 - 0.54)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 21) (EEA/UK, Argentina, Australia, Canada,	21	9.62	101895308	30	563.6	0.05 (0.04 - 0.08)	Observed significantly < expected

Table 54 Observed Versus Expected Analysis for Myocarditis cases within 42 days

Myocarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Chile, Malaysia, Philippines)							
Dose 2 - All cases, all ages (RW 21 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	9.62	101895308	87	563.6	0.15 (0.12 - 0.19)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 42) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	9.62	120426885	217	1332.19	0.16 (0.14 - 0.19)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 42 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	9.62	120426885	366	1332.19	0.27 (0.25 - 0.3)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 42) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	9.62	101895308	45	1127.19	0.04 (0.03 - 0.05)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 42 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	9.62	101895308	101	1127.19	0.09 (0.07 - 0.11)	Observed significantly < expected

EEA European Economic Area, MC Medically confirmed, NC Non-confirmed, RW Risk Window, UK United Kingdom.

The observed versus expected analysis for all reported cases of myocarditis with risk windows 7, 14, 21 and 42 days from vaccination and taking into account different age and gender stratifications suggested that observed cases occurred less frequently than expected, except for age group 18-49 in EU/UK and 30-49 years females and 18-39 years males with risk window 7 days. However, only 4 of the 59 cases in 18-49 age group from EU/UK met the Brighton Criteria Level 1, 2 definition for myocarditis. Based on these 4 cases, O/E analysis suggests less observed cases (4) occurred than expected (43) in this age group.

Mechanism of Action of Myocarditis and COVID-19 VACCINE ASTRAZENECA

Myocarditis is an inflammatory diseases of the heart muscles. The possible mechanism by which COVID-19 VACCINE ASTRAZENECA may cause myocarditis could be related to inflammation, autoimmunity or a combination of both. Co-morbidities may be a contributing factor which could feed into an inflammatory mechanism as pericytes expressing high levels of the ACE2 receptor and levels have been found to be increased in diseases Chen et al 2020 In animal studies with COVID-19 VACCINE ASTRAZEENCA, circulating spike protein was measured and can be detected after vaccination. Inflammation through activation of the innate pathway through dsRNA has also been implicated for mRNA vaccines Milano et al 2021. Whilst dsRNA is not applicable to COVID-19 VACCINE ASTRAZENECA, adenovirus vectors do activate innate pathways which could be another possible explanation for COVID-19 VACCINE ASTRAZENECA Zhu et al 2007, Muruve 2004.

Based on the cumulative review of safety report cases, AstraZeneca opinion is that the MOA for myocarditis is unrelated to COVID-19 VACCINE ASTRAZENECA.

Summary

Out of 593 myocarditis cases there was a preponderance for male gender (49.6%) versus females (47.4%), and 42.8% of cases were for patients between 40 to 65 years old. The majority (69.5%) of cases were reported after the first dose. All (100%) cases were serious with 2.5% resulting in death. 0.8 % case reports fulfilled Brighton collaboration level 1 criteria, 5.6% case reports fulfilled Brighton collaboration level 2 criteria, no case reports fulfilled Brighton collaboration level 3 criteria, 51.3% case reports fulfilled Brighton collaboration level 4 criteria and 42.3% case reports fulfilled Brighton collaboration level 5 criteria. Observed vs expected analysis suggests that observed number of cases regardless of age, gender, and various risk windows did not exceed the expected number of cases. AstraZeneca opinion is that the MOA for myocarditis is unrelated to COVID-19 VACCINE ASTRAZENECA.

15.2.13.2 Pericarditis

Review of Cases

A search of the global patient safety database was conducted for cumulative adverse event data (from 29 December 2020 up to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PTs under SMQ narrow Pericarditis; Autoimmune pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pericarditis lupus; Pericarditis uraemic; Pleuropericarditis in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified 603 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 603 cases, 598 cases were spontaneously reported, 2 cases were from Non-interventional/Post-marketing study (D8111C00004) and 3 cases were from literature. No case was reported from clinical trial. Out of 603 cases, 42 cases were associated with the combined events of Myocarditis and Pericarditis.

Of the 603 cases, 491 (81.4%) cases were serious due to the AE being considered as medically important event (283), the AE resulted in disability (39), AE required hospitalization (277), AE was life threatening (36), AE resulted in death (2) and the remaining 112(18.6%) cases were non-serious. Out of 603 cases 215 (35.7%) were medically confirmed and 388 (64.3%) were consumer reports.

The Outcome of adverse events (AEs) were: 2 (0.3%) Died, 194 (32.2%) Not Recovered, 105 (17.4%) Recovered, 15 (2.5%) Recovered with Sequalae, 189 (31.3%) Recovering and 98 (16.3%) Unknown.

There were 2 (0.3%) cases with fatal outcome (case ID: PPD). These data are summarised in Table 55 below. Case PPD was with combined event of Myocarditis hence data was included in the fatal report of myocarditis (Table 55).

Table 55 Summary of case with fatal outcome for Pericarditis

Sr No	Case ID/ Country/ Case Serious (Y/N) / Medically Confirmed (Y / N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days)/ # Dose	Event / Outcome	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/Causality Assessment
1	PPD / YES / NO	PPD	PPD / Not reported	44	44 / Dose 1	Pericarditis / Died	clogged coronary artery and Inflammation of the pericardium / Yes	Alternative cause included CAD from autopsy finding "clogged coronary artery"; disease risk factor; Limited work-up information reported / Limited information to make any causality assessment

CAD: Coronary artery disease; F, Female; M, Male; N, No Y, Yes

Out of the 603 reports, 215 (35.7%) from the United Kingdom, 160 (26.5%) from Australia, 57 (9.5%) from France, 36 (6.0%) from Italy, 18 (3.0%) cases each from Germany and Netherlands, 16 (2.7%) from Spain, 13 (2.2%) from Belgium, 12 (2.0) from Sweden, 9 (1.5%) from Greece, 7 (1.2%) cases each from Ireland and Portugal, 6 (1.0%) from Brazil, 5 (0.5%) each from Canada and Denmark, 4 (0.7%) from Norway, 2 (0.3%) cases each from Austria, Finland and Romania and 1 (0.2%) case each from [redacted]

There were 307 (50.9%) reports in male vaccinees, 284 (47.1%) were in females and the gender was not reported in 12 (2.0%) cases. The age ranged from 14-89 years; 3 (0.5%) vaccinees were <17 years, 123 (20.4%) vaccinees were in age group of 18 to 40 years, 309 (51.2%) vaccinees were in age group of 40 to 65 years of age, 122 (20.2%) vaccinees were ≥65 years of age and for 46 (7.6%) vaccinees the age was unknown.

The adverse event preferred terms reported as Pericarditis (593) and Pleuropericarditis (10).

In 486 (80.6%) cases pericarditis was reported after the first dose, in 88 (14.6%) cases pericarditis was reported after the second dose of COVID-19 VACCINE ASTRAZENECA and for 29 (4.8%) cases dose information was unknown. Time-to-onset (TTO) was reported for 430 (71.3%) cases and was unknown for 173 (28.7%). The expected TTO for pericarditis is 2-42 days. 288 (70.4%) out of 430 (67.0%) reported TTO cases were within the expected risk window. These data are summarized in Table 56 below.

Table 56 Time to Onset for event pericarditis (From First Dose /Second Dose/Dose Unknown)

Time to Onset of event (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Case (Dose Unknown)	%
0	34	8		7.0
1	28	2		5.0
2	13	4		2.8
3	19	1		3.3
4	17	4		3.5
5	17	3		3.3
6	11			1.8
7	13	5		3.0
8	4	2		1.0
9	13	1		2.3
10	17	3		3.3
11 to 20 days	51	10		10.1
21 to 30 days	40	12		8.6
31 to 40 days	26	1		4.5
41 to 50 days	10	2		2.0
51 to 60 days	16	9		4.1
61 days and above	30	4		5.6
Unknown days (missing)	127	17	29	28.7

The number of cases that met the criteria for Brighton Collaboration's case definition Levels were as follows:

The Brighton collaboration (Pericarditis_Version_1.0.0_15 July 2021) of the pericarditis case definition were used for the review of the data available in the case reports. Based on this approach, out of the 603 cases, none fulfilled level 1 criteria, 22 fulfilled level 2 criteria, 4 fulfilled level 3 criteria, 406 fulfilled level 4 criteria and 171 cases fulfilled level 5 criteria.

Brighton Collaboration Level 1

Of the 603, no case reports fulfilled Brighton collaboration level 1 criteria. To fulfil this classification histopathologic examination of pericardial tissue (autopsy or surgical biopsy) reports are required and be indicative of pericardial inflammation or meets at least 2 of the 3 following criteria: Evidence of abnormal fluid collection or pericardial inflammation by imaging (Echocardiogram, MR, cMR or CT)/EKG shows all 3 abnormalities as listed (Diffuse concave-upward ST-segment elevation/ST-segment depression in aVR/PR-depression throughout the leads (best shown in leads II & V3) without reciprocal ST-segment changes (depressions)) that are new and/or normalize on recovery, one or more (≥1) physical exam finding of pericardial fluid (pericardial friction rub/pulsus paradoxus/distant heart sounds (infants/children).

Brighton Collaboration Level 2

Of the 603, 22 (3.6%) case reports fulfilled Brighton collaboration level 2 criteria. There are 5 cases with combined event of Myocarditis included in the assessment of level 2 above (Table 53). The cases fulfil this classification by symptoms at presentation meets ≥ 1 of the acute chest pain/chest pressure/palpitations/dyspnea after exercise/at rest/lying down/diaphoresis/sudden death or if infant/young child ≥2 of irritability/vomiting/poor feeding/sweating, and at least 1 of the 3 following criteria met for all ages: ≥ 1 EKG change as listed above that is new and/or normalizes on recovery, Imaging (Echo, MR, cMR or CT) shows abnormal pericardial (fluid collection and/or inflammation), physical exam finding(s) of pericardial fluid (pericardial friction rub and/or pulsus paradoxus). There should be no alternative explanation to explain the illness reported. These cases are summarised in Table 57 below.

The reports had limited information to make causality assessment or alternative causal factors were noted.

Table 57 Cases fulfilling Brighton collaboration level 2 for Pericarditis

Sr No	Case ID/ Country/ Case Serious- Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
1	PPD / YES (Medically Important) / YES	PPD	Not Reported / Not Reported	0 / Dose 1	Pericarditis / Not recovered	chest pain, ECHO showed effusion, limited info, TTO<1D / Limited information to make any causality assessment
2	PPD / YES (Hospitalization) / NO	PPD	Not Reported / Not Reported	74 / Dose 1	Pericarditis / Recovering	chest pain, with pericardial effusion (not clear how this was diagnosed). Limited information. TTO >7D. / Limited information to make any causality assessment
3	PPD / YES (Hospitalization and Medically Important) / NO	PPD	PPD	7 / Dose 1	Pericarditis / Recovering	chest pain + Echo confirmed pericarditis; arrythmia + troponin rise. TTO within 7 days / Limited information to make any causality assessment
4	PPD / YES (Hospitalization and LT) / NO	PPD	PPD	4 / Dose 2	Pericarditis / Recovering	CT+ for effusion; coupled w/ chest pain and dyspnoea, CRP / Limited information to make any causality assessment
5	PPD / YES (Hospitalization) / YES	PPD	Not Reported / Not Reported	53 / Dose 1	Pericarditis / Recovering	chest pain, ECG with ST segment elevation, TTO >7days. / Limited information to make any causality assessment
6	PPD / YES (Hospitalization) / NO	PPD	Not Reported / Not Reported	9 / Dose 1	Pericarditis / Not recovered	Cardiac symptoms + ECG/ECHO report / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious-Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
7	PPD / YES (Medically Important) / NO	PPD	PPD / Not reported	17 / Dose 2	Pericarditis / Not recovered	Chest pain / CT / cMRI / Echo findings (Pericardial effusion) / Limited information to make any causality assessment
8	PPD / YES (Hospitalization) / YES	PPD	Not Reported / Not Reported	2 / Dose 1	Pericarditis / Unk	Chest pain + nausea + vomiting + ECG findings (global ST segment elevation) / Limited information to make any causality assessment
9	PPD / YES (Hospitalization Medically Important) / YES	PPD	Not Reported / Not Reported	Unk / Dose 1	Pericarditis / Recovering	Chest pain + ECG (widespread PR depression or ST elevation) / Limited information to make any causality assessment
10	PPD / YES (Hospitalization Medically Important) / NO	PPD	PPD / Not reported	23 / Dose 1	Pericarditis / Recovered	Palpitation + Shortness of Breath (SOB) + Echo (Pericardial effusion) / Limited information to make any causality assessment
11	PPD / YES (Hospitalization and Medically Important) / YES	PPD	Not reported / PPD	1 / Dose 1	Pericarditis / Recovering	Chest pain + EKG findings (ST elevation), Limited info, limited work up info / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious-Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
12	PPD / YES (LT and Medically Important) / YES	PPD	PPD	16 / Dose 1	Pericarditis / Recovering	chest pain + pulsus paradoxus + EKG finding (pulsus paradoxus were unknown, Pericardial effusion) / Limited information to make any causality assessment
13	PPD / YES (Hospitalization and LT) /YES	PPD	Not reported / PPD	4 / Dose 1	Pericarditis / Not recovered	Echo (pericardial effusion) + chest pain; Limited info, limited work up info / Limited information to make any causality assessment
14	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	Unk / Dose 1	Pericarditis / Not recovered	Chest pain + Dyspnoea + ECG, Chest Xray and CT:Pleural effusion / Limited information to make any causality assessment
15	PPD YES (Hospitalization and Medically Important) / YES	PPD	Not Reported / Not Reported	36 / Dose 1	Pericarditis / Unk	Cardiac symptoms (Chest pain) + Follow up echocardiogram 24 hours post removal of drain revealed trivial pericardial effusion, Limited info, limited work up info / Limited information to make any causality assessment
16	PPD / YES (Hospitalization and Medically Important) / NO	PPD	PPD	47 / Dose 2	Pericarditis / Recovering	Cardiac symptom (chest pain + back pain) + echocardiogram was on the basis of CTPA which revealed shallow bilateral pleural effusions and mild cardiomegaly, limited work up info / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious-Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
17	PPD / NO (Non-serious) / YES	PPD	Not Reported / Not Reported	0 / Dose 1	Pericarditis / Not recovered	EKG finding (Electrocardiogram ST segment abnormal) + chest pain; limited work up info / Limited information to make any causality assessment

TTO: Time to onset, cMRI: Magnetic resonance imaging, ECG: electrocardiography EKG: Electrocardiogram, EF: Ejection Fraction, CRP: C-reactive protein, CTPA: CT pulmonary angiogram, CT: Computed tomography, LT: Life threatening; Y, Yes; N, No; M, Male; F, Female

Brighton Collaboration Level 3

Of the 603, 4 (0.7%) case reports fulfilled Brighton collaboration level 3 criteria. These case reports are level 3 based on presence of one of the following factors: Symptoms at presentation meets at least 1 non-specific symptom listed Cough/Edema/Cyanosis/Weakness/Fatigue/Altered mental status/Shoulder +/or upper back pain/Low grade intermittent fever (≥38.0oC)/GI (nausea +/or vomiting +/or diarrhea) and ≥1 of the following: new onset cardiac chest pain or pressure/palpitations/dyspnea after exercise, at rest or lying down; or infant/young child: ≥2 of irritability/vomiting/poor feeding/back pain/tachypnoea, lethargy for all ages : ≥ 1 of the following: chest radiograph shows enlarged heart/non-specific EKG abnormalities that are new and/or normalize on recovery. There should be no alternative explanation to explain the illness reported. These cases are summarised in Table 58 below.

The reports had limited information to make causality assessment or alternative causal factors were noted.

Table 58 Cases fulfilling Brighton collaboration level 3 for Pericarditis

Sr No	Case ID/ Country/ Case Serious- Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
1	PPD / YES (Medically Important) / YES	PPD	Not Reported / Not Reported	0 / Dose 1	Pericarditis / Not recovered	chest pain, ECHO showed effusion, limited info, TTO<1D / Limited information to make any causality assessment
2	PPD / YES (Hospitalization) / NO	PPD	Not Reported / Not Reported	74 / Dose 1	Pericarditis / Recovering	chest pain, with pericardial effusion (not clear how this was diagnosed). Limited information. TTO >7D. / Limited information to make any causality assessment
3	PPD / YES (Hospitalization and Medically Important) / NO	PPD	PPD	7 / Dose 1	Pericarditis / Recovering	chest pain + Echo confirmed pericarditis; arrythmia + troponin rise. TTO within 7 days / Limited information to make any causality assessment
4	PPD / YES (Hospitalization and LT) / NO	PPD	PPD	4 / Dose 2	Pericarditis / Recovering	CT+ for effusion; coupled w/ chest pain and dyspnoea, CRP / Limited information to make any causality assessment
5	PPD / YES (Hospitalization) / YES	PPD	Not Reported / Not Reported	53 / Dose 1	Pericarditis / Recovering	chest pain, ECG with ST segment elevation, TTO >7days. / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious-Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
6	PPD / YES (Hospitalization) / NO	PPD	Not Reported / Not Reported	9 / Dose 1	Pericarditis / Not recovered	Cardiac symptoms + ECG/ECHO report / Limited information to make any causality assessment
7	PPD / YES (Medically Important) / NO	PPD	PPD / Not reported	17 / Dose 2	Pericarditis / Not recovered	Chest pain / CT / cMRI / Echo findings (Pericardial effusion) / Limited information to make any causality assessment
8	PPD / YES (Hospitalization) / YES	PPD	Not Reported / Not Reported	2 / Dose 1	Pericarditis / Unk	Chest pain + nausea + vomiting + ECG findings (global ST segment elevation) / Limited information to make any causality assessment
9	PPD / YES (Hospitalization Medically Important) / YES	PPD	Not Reported / Not Reported	Unk / Dose 1	Pericarditis / Recovering	Chest pain + ECG (widespread PR depression or ST elevation) / Limited information to make any causality assessment
10	PPD / YES (Hospitalization Medically Important) / NO	PPD	PPD / Not reported	23 / Dose 1	Pericarditis / Recovered	Palpitation + Shortness of Breath (SOB) + Echo (Pericardial effusion) / Limited information to make any causality assessment
11	PPD / YES	PPD	Not reported / PPD	1 / Dose 1	Pericarditis / Recovering	Chest pain + EKG findings (ST elevation), Limited info,

Sr No	Case ID/ Country/ Case Serious- Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
	(Hospitalization and Medically Important) / YES					limited work up info / Limited information to make any causality assessment
12	PPD / YES (LT and Medically Important) / YES	PPD	PPD	16 / Dose 1	Pericarditis / Recovering	chest pain + pulsus paradoxus + EKG finding (pulsus paradoxus were unknown, Pericardial effusion) / Limited information to make any causality assessment
13	PPD / YES (Hospitalization and LT) /YES	PPD	Not reported / PPD	4 / Dose 1	Pericarditis / Not recovered	Echo (pericardial effusion) + chest pain; Limited info, limited work up info / Limited information to make any causality assessment
14	PPD / YES (Medically Important) / NO	PPD	Not Reported / Not Reported	Unk / Dose 1	Pericarditis / Not recovered	Chest pain + Dyspnoea + ECG, Chest Xray and CT:Pleural effusion / Limited information to make any causality assessment
15	PPD / YES (Hospitalization and Medically Important) / YES	PPD	Not Reported / Not Reported	36 / Dose 1	Pericarditis / Unk	Cardiac symptoms (Chest pain) + Follow up echocardiogram 24 hours post removal of drain revealed trivial pericardial effusion, Limited info, limited work up info / Limited information to make any causality assessment

Sr No	Case ID/ Country/ Case Serious- Y/N(Seriousness) / Medically Confirmed (Y/N)	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days)/# Dose	Event / Outcome	Additional Comment/Causality Assessment
16	PPD / YES (Hospitalization and Medically Important) / NO	PPD	PPD	47 / Dose 2	Pericarditis / Recovering	Cardiac symptom (chest pain + back pain) + echocardiogram was on the basis of CTPA which revealed shallow bilateral pleural effusions and mild cardiomegaly, limited work up info / Limited information to make any causality assessment
17	PPD / NO (Non-serious) / YES	PPD	Not Reported / Not Reported	0 / Dose 1	Pericarditis / Not recovered	EKG finding (Electrocardiogram ST segment abnormal) + chest pain; limited work up info / Limited information to make any causality assessment

TTO: Time to onset, CT: Computed tomography; Y, Yes; N, No; M, Male; F, Female

Brighton Collaboration Level 4

Based on the review, 406 (67.3%) out of 603 cases were classified as Brighton collaboration level 4. These cases failed to meet level 3, 2 of the case definitions because test(s) were not done or results unknown or history/physical exam features were not documented.

Brighton Collaboration 5

Based on the review, 171 (28.4%) out of 603 cases were classified as Brighton collaboration level 5 (ie, Pericarditis excluded due to an alternative diagnosis).

Generally, there was too limited information in many case reports to make an informed assessment of causality or conclude on the presence of confounding factors.

Observed vs. Expected Analysis

An Observed versus Expected (O/E) analyses have been conducted for pericarditis cases (medically confirmed and not confirmed) received by the DLP of 28 December 2021. The expected TTO for pericarditis is 2-42 days. The data are stratified by age categories (18–49 years, 50–59 years, 60–69 years, 70–79 years, ≥ 80 years), gender, for various risk windows (7 days, 14 days, 21 days, and 42 days) and with dose details (dose 1 and dose 2 for regions EEA, United Kingdom, Argentina, Australia, Canada, Chile, Malaysia and Philippines).

O/E analyses for cases of pericarditis are shown below in Table 59. Background incidence rates from Truven Marketscan (2019) have been used for O/E analyses. These include hospitalized and non-hospitalized cases pericarditis cases.

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis - All cases, all ages (RW 7) MC and NC	7	26.38	291626957	179	1474.41	0.12 (0.1 - 0.14)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 14) MC and NC	14	26.38	291626957	245	2948.83	0.08 (0.07 - 0.09)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 21) MC and NC	21	26.38	291626957	289	4423.24	0.07 (0.06 - 0.07)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 42) MC and NC	42	26.38	291626957	360	8846.48	0.04 (0.04 - 0.05)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 7+Unk) MC and NC	7	26.38	291626957	345	1474.41	0.23 (0.21 - 0.26)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 14+Unk) MC and NC	14	26.38	291626957	411	2948.83	0.14 (0.13 - 0.15)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 21+Unk) MC and NC	21	26.38	291626957	455	4423.24	0.1 (0.09 - 0.11)	Observed significantly < expected
Pericarditis - All cases, all ages (RW 42+Unk) MC and NC	42	26.38	291626957	526	8846.48	0.06 (0.05 - 0.06)	Observed significantly < expected
Pericarditis - All ages (RW 7) MC	7	26.38	291626957	74	1474.41	0.05 (0.04 - 0.06)	Observed significantly < expected
Pericarditis - All ages (RW 14) MC	14	26.38	291626957	94	2948.83	0.03 (0.03 - 0.04)	Observed significantly < expected
Pericarditis - All ages (RW 21) MC	21	26.38	291626957	107	4423.24	0.02 (0.02 - 0.03)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis - All ages (RW 42) MC	42	26.38	291626957	137	8846.48	0.02 (0.01 - 0.02)	Observed significantly < expected
Pericarditis - All ages (RW 7+Unk) MC	7	26.38	291626957	125	1474.41	0.08 (0.07 - 0.1)	Observed significantly < expected
Pericarditis - All ages (RW 14+Unk) MC	14	26.38	291626957	145	2948.83	0.05 (0.04 - 0.06)	Observed significantly < expected
Pericarditis - All ages (RW 21+Unk) MC	21	26.38	291626957	158	4423.24	0.04 (0.03 - 0.04)	Observed significantly < expected
Pericarditis - All ages (RW 42+Unk) MC	42	26.38	291626957	188	8846.48	0.02 (0.02 - 0.02)	Observed significantly < expected
Pericarditis 18-49 (EEA/UK) MC and NC	7	20.35	27716022	49	108.1	0.45 (0.34 - 0.6)	Observed significantly < expected
Pericarditis 50-59 (EEA/UK) MC and NC	7	27.87	19552392	37	104.44	0.35 (0.25 - 0.49)	Observed significantly < expected
Pericarditis 60-69 (EEA/UK) MC and NC	7	39.1	28510714	25	213.65	0.12 (0.08 - 0.17)	Observed significantly < expected
Pericarditis 70-79 (EEA/UK) MC and NC	7	52.6	14795684	19	149.15	0.13 (0.08 - 0.2)	Observed significantly < expected
Pericarditis ≥ 80 (EEA/UK) MC and NC	7	67.63	3858135	1	50.01	0.02 (0 - 0.11)	Observed significantly < expected
Pericarditis 18-49 (EEA/UK) MC and NC	14	20.35	27716022	68	216.19	0.31 (0.24 - 0.4)	Observed significantly < expected
Pericarditis 50-59 (EEA/UK) MC and NC	14	27.87	19552392	49	208.87	0.23 (0.17 - 0.31)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis 60-69 (EEA/UK) MC and NC	14	39.1	28510714	36	427.3	0.08 (0.06 - 0.12)	Observed significantly < expected
Pericarditis 70-79 (EEA/UK) MC and NC	14	52.6	14795684	23	298.31	0.08 (0.05 - 0.12)	Observed significantly < expected
Pericarditis ≥ 80 (EEA/UK) MC and NC	14	67.63	3858135	2	100.01	0.02 (0 - 0.07)	Observed significantly < expected
Pericarditis 18-49 (EEA/UK) MC and NC	21	20.35	27716022	78	324.29	0.24 (0.19 - 0.3)	Observed significantly < expected
Pericarditis 50-59 (EEA/UK) MC and NC	21	27.87	19552392	59	313.31	0.19 (0.14 - 0.24)	Observed significantly < expected
Pericarditis 60-69 (EEA/UK) MC and NC	21	39.1	28510714	48	640.95	0.07 (0.06 - 0.1)	Observed significantly < expected
Pericarditis 70-79 (EEA/UK) MC and NC	21	52.6	14795684	25	447.46	0.06 (0.04 - 0.08)	Observed significantly < expected
Pericarditis ≥ 80 (EEA/UK) MC and NC	21	67.63	3858135	2	150.02	0.01 (0 - 0.05)	Observed significantly < expected
Pericarditis 18-49 (EEA/UK) MC and NC	42	20.35	27716022	98	648.58	0.15 (0.12 - 0.18)	Observed significantly < expected
Pericarditis 50-59 (EEA/UK) MC and NC	42	27.87	19552392	74	626.62	0.12 (0.09 - 0.15)	Observed significantly < expected
Pericarditis 60-69 (EEA/UK) MC and NC	42	39.1	28510714	59	1281.9	0.05 (0.04 - 0.06)	Observed significantly < expected
Pericarditis 70-79 (EEA/UK) MC and NC	42	52.6	14795684	33	894.93	0.04 (0.03 - 0.05)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis ≥ 80 (EEA/UK) MC and NC	42	67.63	3858135	4	300.04	0.01 (0 - 0.03)	Observed significantly < expected
Pericarditis Female 18 to 29 (UK) MC and NC	7	13.84	1339334	2	3.55	0.56 (0.07 - 2.04)	Observed < expected
Pericarditis Female 30 to 39 (UK) MC and NC	7	16.55	2096348	6	6.65	0.9 (0.33 - 1.96)	Observed < expected
Pericarditis Female 40 to 49 (UK) MC and NC	7	16.98	4974220	8	16.19	0.49 (0.21 - 0.97)	Observed significantly < expected
Pericarditis Female 50 to 59 (UK) MC and NC	7	25.2	6319086	7	30.52	0.23 (0.09 - 0.47)	Observed significantly < expected
Pericarditis Female 60 to 69 (UK) MC and NC	7	32.25	4859019	4	30.03	0.13 (0.04 - 0.34)	Observed significantly < expected
Pericarditis Female 70 to 79 (UK) MC and NC	7	45.51	3562147	0	31.07	0 (0 - 0.12)	Observed significantly < expected
Pericarditis Female 80 plus (UK) MC and NC	7	66.8	1721795	0	22.04	0 (0 - 0.17)	Observed significantly < expected
Pericarditis Male 18 to 29 (UK) MC and NC	7	27.33	986375	0	5.17	0 (0 - 0.71)	Observed significantly < expected
Pericarditis Male 30 to 39 (UK) MC and NC	7	23.71	1582807	3	7.19	0.42 (0.09 - 1.22)	Observed < expected
Pericarditis Male 40 to 49 (UK) MC and NC	7	24.28	5220928	9	24.29	0.37 (0.17 - 0.7)	Observed significantly < expected
Pericarditis Male 50 to 59 (UK) MC and NC	7	30.85	6957211	7	41.13	0.17 (0.07 - 0.35)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis Male 60 to 69 (UK) MC and NC	7	46.7	4966917	3	44.45	0.07 (0.01 - 0.2)	Observed significantly < expected
Pericarditis Male 70 to 79 (UK) MC and NC	7	60.94	3223317	2	37.65	0.05 (0.01 - 0.19)	Observed significantly < expected
Pericarditis Male 80 plus (UK) MC and NC	7	68.8	1042292	0	13.74	0 (0 - 0.27)	Observed significantly < expected
Pericarditis Female 18 to 29 (UK) MC and NC	14	13.84	1339334	2	7.11	0.28 (0.03 - 1.02)	Observed < expected
Pericarditis Female 30 to 39 (UK) MC and NC	14	16.55	2096348	8	13.3	0.6 (0.26 - 1.19)	Observed < expected
Pericarditis Female 40 to 49 (UK) MC and NC	14	16.98	4974220	10	32.37	0.31 (0.15 - 0.57)	Observed significantly < expected
Pericarditis Female 50 to 59 (UK) MC and NC	14	25.2	6319086	10	61.04	0.16 (0.08 - 0.3)	Observed significantly < expected
Pericarditis Female 60 to 69 (UK) MC and NC	14	32.25	4859019	4	60.07	0.07 (0.02 - 0.17)	Observed significantly < expected
Pericarditis Female 70 to 79 (UK) MC and NC	14	45.51	3562147	0	62.14	0 (0 - 0.06)	Observed significantly < expected
Pericarditis Female 80 plus (UK) MC and NC	14	66.8	1721795	0	44.09	0 (0 - 0.08)	Observed significantly < expected
Pericarditis Male 18 to 29 (UK) MC and NC	14	27.33	986375	0	10.33	0 (0 - 0.36)	Observed significantly < expected
Pericarditis Male 30 to 39 (UK) MC and NC	14	23.71	1582807	3	14.38	0.21 (0.04 - 0.61)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis Male 40 to 49 (UK) MC and NC	14	24.28	5220928	14	48.59	0.29 (0.16 - 0.48)	Observed significantly < expected
Pericarditis Male 50 to 59 (UK) MC and NC	14	30.85	6957211	10	82.27	0.12 (0.06 - 0.22)	Observed significantly < expected
Pericarditis Male 60 to 69 (UK) MC and NC	14	46.7	4966917	3	88.91	0.03 (0.01 - 0.1)	Observed significantly < expected
Pericarditis Male 70 to 79 (UK) MC and NC	14	60.94	3223317	4	75.29	0.05 (0.01 - 0.14)	Observed significantly < expected
Pericarditis Male 80 plus (UK) MC and NC	14	68.8	1042292	1	27.49	0.04 (0 - 0.2)	Observed significantly < expected
Pericarditis Female 18 to 29 (UK) MC and NC	21	13.84	1339334	2	10.66	0.19 (0.02 - 0.68)	Observed significantly < expected
Pericarditis Female 30 to 39 (UK) MC and NC	21	16.55	2096348	8	19.95	0.4 (0.17 - 0.79)	Observed significantly < expected
Pericarditis Female 40 to 49 (UK) MC and NC	21	16.98	4974220	12	48.56	0.25 (0.13 - 0.43)	Observed significantly < expected
Pericarditis Female 50 to 59 (UK) MC and NC	21	25.2	6319086	12	91.56	0.13 (0.07 - 0.23)	Observed significantly < expected
Pericarditis Female 60 to 69 (UK) MC and NC	21	32.25	4859019	5	90.1	0.06 (0.02 - 0.13)	Observed significantly < expected
Pericarditis Female 70 to 79 (UK) MC and NC	21	45.51	3562147	0	93.21	0 (0 - 0.04)	Observed significantly < expected
Pericarditis Female 80 plus (UK) MC and NC	21	66.8	1721795	0	66.13	0 (0 - 0.06)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis Male 18 to 29 (UK) MC and NC	21	27.33	986375	1	15.5	0.06 (0 - 0.36)	Observed significantly < expected
Pericarditis Male 30 to 39 (UK) MC and NC	21	23.71	1582807	3	21.58	0.14 (0.03 - 0.41)	Observed significantly < expected
Pericarditis Male 40 to 49 (UK) MC and NC	21	24.28	5220928	18	72.88	0.25 (0.15 - 0.39)	Observed significantly < expected
Pericarditis Male 50 to 59 (UK) MC and NC	21	30.85	6957211	14	123.4	0.11 (0.06 - 0.19)	Observed significantly < expected
Pericarditis Male 60 to 69 (UK) MC and NC	21	46.7	4966917	7	133.36	0.05 (0.02 - 0.11)	Observed significantly < expected
Pericarditis Male 70 to 79 (UK) MC and NC	21	60.94	3223317	4	112.94	0.04 (0.01 - 0.09)	Observed significantly < expected
Pericarditis Male 80 plus (UK) MC and NC	21	68.8	1042292	1	41.23	0.02 (0 - 0.14)	Observed significantly < expected
Pericarditis Female 18 to 29 (UK) MC and NC	42	13.84	1339334	4	21.32	0.19 (0.05 - 0.48)	Observed significantly < expected
Pericarditis Female 30 to 39 (UK) MC and NC	42	16.55	2096348	8	39.9	0.2 (0.09 - 0.4)	Observed significantly < expected
Pericarditis Female 40 to 49 (UK) MC and NC	42	16.98	4974220	17	97.12	0.18 (0.1 - 0.28)	Observed significantly < expected
Pericarditis Female 50 to 59 (UK) MC and NC	42	25.2	6319086	13	183.11	0.07 (0.04 - 0.12)	Observed significantly < expected
Pericarditis Female 60 to 69 (UK) MC and NC	42	32.25	4859019	6	180.2	0.03 (0.01 - 0.07)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Pericarditis Female 70 to 79 (UK) MC and NC	42	45.51	3562147	0	186.42	0 (0 - 0.02)	Observed significantly < expected
Pericarditis Female 80 plus (UK) MC and NC	42	66.8	1721795	0	132.26	0 (0 - 0.03)	Observed significantly < expected
Pericarditis Male 18 to 29 (UK) MC and NC	42	27.33	986375	3	31	0.1 (0.02 - 0.28)	Observed significantly < expected
Pericarditis Male 30 to 39 (UK) MC and NC	42	23.71	1582807	4	43.15	0.09 (0.03 - 0.24)	Observed significantly < expected
Pericarditis Male 40 to 49 (UK) MC and NC	42	24.28	5220928	21	145.77	0.14 (0.09 - 0.22)	Observed significantly < expected
Pericarditis Male 50 to 59 (UK) MC and NC	42	30.85	6957211	17	246.81	0.07 (0.04 - 0.11)	Observed significantly < expected
Pericarditis Male 60 to 69 (UK) MC and NC	42	46.7	4966917	7	266.73	0.03 (0.01 - 0.05)	Observed significantly < expected
Pericarditis Male 70 to 79 (UK) MC and NC	42	60.94	3223317	5	225.88	0.02 (0.01 - 0.05)	Observed significantly < expected
Pericarditis Male 80 plus (UK) MC and NC	42	68.8	1042292	1	82.46	0.01 (0 - 0.07)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 7) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	26.38	120426885	146	608.86	0.24 (0.2 - 0.28)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 7 + Unk) (EEA/UK, Argentina, Australia,	7	26.38	120426885	271	608.86	0.45 (0.39 - 0.5)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Canada, Chile, Malaysia, Philippines)							
Dose 2 - All cases, all ages (RW 7) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	26.38	101895308	27	515.16	0.05 (0.03 - 0.08)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 7 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	7	26.38	101895308	44	515.16	0.09 (0.06 - 0.11)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 14) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	26.38	120426885	203	1217.71	0.17 (0.14 - 0.19)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 14 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	26.38	120426885	328	1217.71	0.27 (0.24 - 0.3)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 14) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	26.38	101895308	35	1030.33	0.03 (0.02 - 0.05)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Dose 2 - All cases, all ages (RW 14 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	14	26.38	101895308	52	1030.33	0.05 (0.04 - 0.07)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 21) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	26.38	120426885	238	1826.57	0.13 (0.11 - 0.15)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 21 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	26.38	120426885	363	1826.57	0.2 (0.18 - 0.22)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 21) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	26.38	101895308	44	1545.49	0.03 (0.02 - 0.04)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 21 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	21	26.38	101895308	61	1545.49	0.04 (0.03 - 0.05)	Observed significantly < expected
Dose 1 - All cases, all ages (RW 42) (EEA/UK, Argentina, Australia,	42	26.38	120426885	297	3653.14	0.08 (0.07 - 0.09)	Observed significantly < expected

Table 59 Observed Versus Expected Analysis for Pericarditis cases within 42 days

Pericarditis by age groups (years) and gender	Risk window (days)	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Canada, Chile, Malaysia, Philippines)							
Dose 1 - All cases, all ages (RW 42 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	26.38	120426885	422	3653.14	0.12 (0.1 - 0.13)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 42) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	26.38	101895308	56	3090.99	0.02 (0.01 - 0.02)	Observed significantly < expected
Dose 2 - All cases, all ages (RW 42 + Unk) (EEA/UK, Argentina, Australia, Canada, Chile, Malaysia, Philippines)	42	26.38	101895308	73	3090.99	0.02 (0.02 - 0.03)	Observed significantly < expected

MC: Medically confirmed, NC: Non-confirmed; F, Female; M, Male; N, No; Y, Yes

The observed number of cases regardless of age, gender, and various risk windows, for pericarditis did not exceed the expected number of cases.

Summary

Out of 603 pericarditis cases there was a preponderance for male gender (50.9%) versus females (47.1%), and 51.2% of cases were for patients between 40 to 65 years old. The majority (69.5%) of cases were reported after the first dose. The majority of cases (81.4%) were serious with 0.3% resulting in death. No case reports fulfilled Brighton collaboration level 1 criteria, 3.6 % case reports fulfilled Brighton collaboration level 2 criteria, 0.7% case reports fulfilled Brighton collaboration level 3 criteria, 67.3% case reports fulfilled Brighton collaboration level 4 criteria and 28.4% case reports fulfilled Brighton collaboration level 5 criteria. Observed vs expected analysis suggests that observed number of cases regardless of age, gender, and various risk windows did not exceed the expected number of cases.

15.2.13.3 Myocarditis and Pericarditis Literature review

A search of the literature was completed to review the occurrence of Myocarditis and Pericarditis in association with COVID-19 VACCINE ASTRAZENECA and other COVID-19 vaccines through 28 December 2021. The searches were conducted in the Embase, and InsightMeme databases. The searches yielded 239 articles, including those previously discussed. Update of relevant literature article findings from this search are discussed and presented below:

- The largest study to date of acute cardiac outcomes after COVID-19 vaccination or SARS-CoV-2 infection was published by Patone et al 2021 on 14 December 2021: "Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection". The study investigated hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias within 28 days following at least one vaccination with AZD1222 (n=20,615,911), BNT162b2 (n=16,993,389) or mRNA-1273 (n=1,006,191), or following a SARS-CoV-2 positive test (n=3,028,867) in people aged ≥16 years in England. It was estimated that there was an extra 2, 1 and 6 myocarditis events/million people vaccinated within 28 days of the first respective doses of AZD1222, BNT162b2 and mRNA-1273, and an extra 10 events/million after a second dose of mRNA-1273. Comparatively, an extra 40 myocarditis events/million were observed within 28 days of a SARS-CoV-2 positive test. An increased risk of pericarditis and arrhythmia were observed within 28 days of a positive SARS-CoV-2 test (6 and 2400 events/million, respectively), and arrhythmia following the second dose of mRNA-1273 (41 events/million). The authors concluded that there was no increased risk of pericarditis or arrhythmia following AZD1222 or BNT162b2.

  AstraZeneca Comment: No increased risk of pericarditis or arrhythmia was observed following COVID-19 VACCINE ASTRAZENECA vaccination, while increased risks were observed following a positive SARS-CoV-2 test. Also a substantially higher risk of

myocarditis was observed following a SARS-CoV-2 positive test than following immunization with COVID-19 VACCINE ASTRAZENECA.

- Azdaki et al 2021 published an article (Case number: PPD) on "Long QT interval and syncope after a single dose of COVID-19 vaccination: A case report.". This is a case report of a PPD year old PPD with a medical history of PPD who developed 1-2 minutes of consecutive syncope attack (QTc 600ms) 3 days after first COVID-19 AstraZeneca vaccine.

  AstraZeneca Comment: This is not considered as a strong case for development of myocarditis after exposure to COVID-19 VACCINE ASTRAZENECA considering the risk factor of age (PPD years old), underlying condition of cardiovascular disease (hypertension), and limited information on concomitant medications, baseline status of the mentioned premorbid disease conditions and other possible causes of long QT interval such as diarrhea, low serum magnesium, low serum potassium, malnourishment, and chronic alcoholism. This case was assessed as BC4 under Brighton Collaboration (BC) classification.

- Hung et al 2022 published "A case of myopericarditis with pleuritis in a PPD year old PPD following one week after AstraZeneca covid-19 vaccination". Limited information was provided in the article to ascertain elimination of alternative causality explanation and possible differentials. There was lack of information regarding family history of autoimmune diseases considering it was mentioned in the article that patient's Rheumatoid factor was elevated which is usually found in patients with Rheumatoid arthritis especially values above 20 IU/ml, as in this patient. Also, there was evidence of leucocytosis with neutrophil predominance in the blood which is an evidence of ongoing infectious process. The culture study performed for the exudate pleural effusion with neutrophil predominance leucocytosis was stated to be negative, however the specific number of days waited for growth was not mentioned.

  AstraZeneca comment: The lack of information regarding the family history, laboratory work up and other possible differentials that could have been ruled out in this article, make it difficult to ascertain causal association of myopericarditis with pleuritis resulting from the use of COVID-19 VACCINE AstraZeneca in this patient. This case had not met database cut-off and is still being processed.

Literature Review Summary

As pointed out in Patone et al 2021. article, which is the largest study carried out to date of acute cardiac outcomes after COVID-19 vaccination or SARS-CoV-2 infection, that no increased risks of pericarditis or arrhythmia have been observed following COVID-19 VACCINE ASTRAZENECA vaccination, while increased risks were observed following a positive SARS-

CoV-2 test, and there has been substantially higher risk of myocarditis observed following a SARS-CoV-2 positive test than following immunization with AZD1222. This findings align with our observation of the case reports we have assessed to date.

Conclusion for Myocarditis and Pericarditis

There were too limited information in many case reports for myocarditis and pericarditis to make an informed assessment of causality or conclude on the presence of confounding factors. AstraZeneca did not find evidence of a new or emerging signal for myocarditis to suggest a need to update the COVID-19 VACCINE ASTRAZENECA CDS or RMP. Myocarditis and pericarditis will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts.

15.2.14 Neuralgic amyotrophy

Request

AstraZeneca received the following request from PRAC in the AR for the 7th SSRs (review period: 01 August 2021 – 30 September 2021):

"Neuralgic amyotrophy: The MAH is requested to perform a cumulative review of cases reporting Neuralgic amyotrophy in the next PSUR, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccine. Cases of neuralgic amyotrophy (Parsonage-Turner Syndrome) should also be searched from the literature. Based on this review, a discussion on the need to update the product information should be provided, if applicable."

AstraZeneca's response to this request is provided below.

Review of cases

A search of the global patient safety database was conducted for cumulative adverse event data through 28 December 2021 using PT: Neuralgic Amyotrophy in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified 53 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 53 cases, 51 cases were spontaneously reported, 1 case was from literature, and 1 case was from post-marketing solicited reports (study D8111C00004, Post-authorization active surveillance of the Safety of COVID-19 Vaccines in the PPD, A consortium study concerning a PPD-year-old PPD who received first dose of Covid-19 Vaccine AstraZeneca and experienced PPD 2 days later. The reporting physician reported that the patient had an illness, pre-existing condition (pins and needles and shoulder pain), or risk factor that could have contributed to the event. No further clinical details, including investigation

findings and treatment details, were provided. After 1 week, patient recovered from the event. The patient received 2nd Dose of AZD1222 vaccine after 70 days of the first dose).

Of the 53 cases, 40 (75.5%) cases were serious due to the AE being considered as medically important (25), the AE resulted in disability (9), AE required hospitalization (11), AE was life threatening (2). Cases may have met more than one criterion for seriousness. The remaining 13 (24.5%) were non-serious. 23 (43.4%) cases were reported by healthcare professionals (medically confirmed) and 30 (56.6%) cases were not medically confirmed consumer reports. The adverse events outcome was as follows: 29 (54.7%) cases were Not recovered, 1 (1.9%) case was Recovered within 8 days, 1 (1.9%) case was Recovered with Sequelae on an unspecified date, 17 (32.1%) cases were Recovering and 5 (9.4%) were reported as Unknown outcome. No case had a fatal outcome.

Of the 53 cases, in 1 of them the outcome was reported as “Recovered” having a time of duration as 8 days. There is, as well other case with outcome reported as “Recovered with Sequelae”, time of duration, however, was reported as “Unknown”.

Table 60 Outcome for Neuralgic Amyotrophy with COVID-19 VACCINE ASTRAZENECA - Cumulative Period through 28 December 2021 (n = 53)

Case Outcome	Number of Cases	%
Not Recovered	29	54.7
Recovered	1	1.9
Recovered with Sequelae	1	1.9
Recovering	17	32.1
Unknown	5	9.4

Out of the 53 reports, 13 (24.5%) cases each were from the UK and Germany, 9 (17%) cases from France, 6 (11.3%) from Netherlands, 5 (9.4%) from Italy, 3 (5.7%) from Austria, and 1 (1.9%) report each from [redacted]

There were 27 (50.9%) reports in female vaccinees, 26 (49.1%) were in males. The age range was 25-83 years; 41 (77.4%) vaccinees were in age group of 18-<65 years of age, 9 (17.0%) vaccinees were >65 years of age, and for 3 (5.7%) vaccinees the age was unknown. The median age was 55 years.

In 6 case reports, the events were reported to have occurred after the second dose of vaccine. The range of TTO for all 53 cases was 0-156 days and median TTO was found to be 10.5 days. The range for those 6 cases after dose 2 were found to be 13-156 days and median TTO was 10 days.

Time to onset (TTO) for the NA events with dose 1 and dose 2 is shown below (Table 61):

Table 61 TTO for Neuralgic Amyotrophy by First and Second Dose of COVID-19 VACCINE ASTRAZENECA - Cumulative Period through 28 December 2021 (n = 53)

Time to Onset of Event (Days)	No. of Cases (From First Dose)	No. of Cases (From Second Dose)	No. of Cases (Dose Unknown)	%
00 Under 1 day	3	0	0	5.7
01 day	4	0	0	7.5
02 days	2	0	0	3.8
03 days	3	0	0	5.7
04 days	3	0	0	5.7
07 days	3	0	0	5.7
08 days	2	0	0	3.8
09 days	1	0	0	1.9
10 to 20 days	10	2	1	24.5
21 to 30 days	3	1	0	7.5
31 to 40 days	3	0	0	5.7
41 to 50 days	2	0	0	3.8
61 days and above	1	2	1	7.5
Unknown days (missing)	4	1	1	11.3

NA, Neuralgic Amyotrophy; TTO, Time to onset

Among all cases, there were 8 cases that had relevant medical history and concomitant medications as risk factors, including: clavicle fracture (1), arthroplasty of knee and Quincke's edema (1), Cervical neuralgia (1), Psoriasis (1), COVID-19 (1), spinal canal stenosis and psoriatic arthritis (1), brachial Plexus neuritis (3), Rotator cuff rupture right (1), Drug allergy (2), Neuralgic amyotrophy (1), Pins and needles (1), shoulder pain (2), Degenerative disc disease and fibromyalgia (1).

Based on the WHO-UMC causality assessment, out of the 53 cases, 24 were considered to be ‘Possible’ due to time to onset within 5 to 30 days from vaccination; (2 cases had risk factors and remaining 22 had limited information such as medical history, concomitant drugs, other differential diagnosis workup), 24 considered to be ‘Unlikely’ and 5 considered to be ‘Unassessable/Unclassifiable.’

Literature

A search of Embase, InsightMeme and PubMed databases were undertaken on 28 December 2021 using the following combination of search terms: Neuralgic Amyotrophy or Parsonage-Turner Syndrome and COVID- 19 vaccines in general, with an interest in the

mechanism of action or any hypothesis that COVID-19 vaccines may trigger this type of syndrome.

The search yielded 9 results and revealed no conclusive mechanism of action for the potential triggering role of COVID-19 VACCINE ASTRAZENECA or other Covid 19 vaccines in Neuralgic Amyotrophy (NA) episodes. From the 9 articles provided, 3 of them were duplicates, 1 was in regard to mRNA vaccines, 2 of them included COVID-19 vaccine but with no specification, 1 in regard to COVID-19 infection and NA.

- Noseda et al 2021 contained a discussion based on disproportionality analyses in VigiBase. The publication compared the frequency where Neuralgic Amyotrophy (NA), Facial paralysis/Bell's Palsy (FP/BP), and Guillain-Barre Syndrome (GBS) that can be disproportionately more frequently reported with COVID-19 vaccines than other viral vaccines. The authors found that all the safety reports in regards to the use of COVID-19 vaccines reached on VigiBase, 0.01% reported NA, in general more frequently reported by physicians, involving more female patients than males, with a median age of 49-years-old. Pfizer-BioNTech COVID-19 vaccine was the most frequently suspected COVID-19 vaccine for NA (66.7%), following by Moderna COVID-19 vaccine (24.6%), AstraZeneca COVID-19 vaccine (8.8%), and with less frequency reported with Janssen COVID-19 vaccine. However, in the disproportionality analyses performed for NA by the authors, overall, no signals of disproportionate reporting with COVID-19 vaccine were detected against either other viral vaccines (ROR 0.23, 95% Cl 0.17-0.30) or influenza vaccines (ROR 0.12, 95% Cl 0.09-0.16), neither sex nor age emerged as risk factors for disproportionate reporting of NA with COVID-19 vaccines, compared wither to other viral vaccines or to influenza vaccines).

AstraZeneca Comment: As mentioned by the authors, there is lacking information on the exact numbers of patients exposed to certain vaccine, since VigiBase does not allow defining incidence of adverse event, also there is no information in regards diagnosis workup, or patient clinical manifestation. No relatedness has been identified between AstraZeneca COVID-19 vaccine and Neuralgic Amyotrophy.

A case described in 1 of the article is summarised below.

- Burillo et al 2021 (case ID: PPD) provided information about a PPD -years-old PPD patient reportedly experienced the intense pain in the left shoulder, radiating to the scapular region and arm, pain persisted during rest and was exacerbated by movement 4 days after vaccination. An MRI study of the shoulder showed mild left subacromial tendinopathy; a cervical MRI scan detected no abnormalities. Electromyography showed fibrillations and positive waves in the extensor digitorum communis, abductor digiti minimi, first dorsal interosseous and abductor pollicis brevis muscles. Patient started treatment with PPD followed by PPD

dosed at PPD for 10 days, with subsequent reduction by PPD, until suspension. Improvement was noted, then after 2 weeks event resolved.

AstraZeneca Comment: Based on the information reported, causality by WHO-UMC classification was assessed as Possible due to temporal association (4 days); however, there is no sufficient information provided about the patient's medical history, concomitant medications, predisposing factors, or differential diagnosis work-up.

Summary

This review provided data on neuralgic amyotrophy for the Cumulative period of up to 28 December 2021 from all COVID-19 VACCINE ASTRAZENECA case reports currently available to AstraZeneca.

Cumulative review of 53 case reports for neuralgic amyotrophy received and analysed by AstraZeneca, there was no predominancy in genders, the median age was 55 years old, and time to onset was 10.5 days. Most cases were reported as serious, but in general had limited information and/or were confounded by alternative aetiologies, including COVID-19 infection. In addition, literature review did not identify any significant new information.

Conclusion

Based on the currently available data, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and neuralgic amyotrophy. No updates to the COVID-19 VACCINE ASTRAZENECA CDS or RMP are warranted.

AstraZeneca will continue to monitor safety data of neuralgic amyotrophy and related terms from all available sources as part of the routine safety surveillance.

15.2.15 Pulmonary embolism (PE) without thrombocytopenia

Request

In the AR for the 8th SSR (review period: 01 October 2021 – 30 November 2021), AstraZeneca identified the following comment from PRAC:

"This topic [Pulmonary embolism (PE) without thrombocytopenia] will continue to be monitored in the upcoming PSURs."

AstraZeneca has provided an updated cumulative review of DVT without thrombocytopenia below

Review of Cases

A cumulative search of the AstraZeneca safety database was undertaken for AE reports received for COVID-19 VACCINE ASTRAZENECA through 28 December 2021 containing the following MedDRA PTs: Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary microemboli, Pulmonary oil microembolism, Pulmonary thrombosis, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis and Pulmonary infarction.

A total of 5199 cases were identified using the above search strategy.

To identify the cases of PE without co-reported thrombocytopenia, the following cases were excluded from the search results described above: any cases with events from the HLT "Thrombocytopenias", SMQ "Hematopoietic thrombocytopenia (Narrow)", or cases with platelet values less than 150,000 per microliter.

After applying the exclusion criteria, 4495 cases of PE without thrombocytopenia remained for further analysis.

The reported PE PTs from the 4495 cases were: Pulmonary embolism (4469), Pulmonary thrombosis (114), Pulmonary infarction (69), Pulmonary artery thrombosis (14), Pulmonary microemboli (6), Pulmonary venous thrombosis (6), and Pulmonary oil microembolism (2).

Of the 4495 case reports, all were serious and 2875 (64.0%) were medically confirmed. The seriousness criteria for the 4495 serious cases of DVT without thrombocytopenia included: Death (293), Life-threatening (1162), Hospitalization or prolongation of existing hospitalization (2664), Persistent or significant disability or incapacity (203), Congenital anomaly (1) and Medically significant (2497). A single case may have met more than one criteria for seriousness.

Of the 4495 cases, 1524 (33.9%) were reported from UK and 921 (20.5%) were reported from Australia. A total of 2293 (51.0%) case reports were reported in females, 2117 (47.1%) were reported in males, and in 85 (1.9%) the gender was not reported. Out of 4495 reported cases, 2110 (46.9%) occurred in adults (18-64 years of age) with median age of 54 years, 2057 (45.8%) in elderly (≥ 65 years of age) with median age 73 years, and in 328 (7.3%) the age was not reported. The median age was 65 years (for all cases; range 18 to 103 years.

Of the 4495 case reports, 293 (6.5%) cases had a fatal outcome. There were 149 medically confirmed cases and 144 non-medically confirmed cases with a fatal outcome. Of the 293 fatal cases, 33 (11.3%) occurred in the age group of 18-49. Age/gender and percentage of the total cases for the fatal reports is presented in Table 62.

Table 62 Pulmonary Embolism Without Thrombocytopenia Case Reports by age/gender, and fatality

Age group	Female N (Fatal cases) Fatal%	Male N (Fatal cases) Fatal%	Gender Unknown N (Fatal cases) Fatal%	Total N (Fatal cases) Fatal%
Age - 18-29 Years	87 (2) 2.4%	28 (1) 3.8%	2 (0) 0%	113 (3) 2.7%
Age - 30-39 Years	135 (8) 6.1%	92 (4) 4.8%	1 (0) 0%	216 (12) 5.6%
Age - 40-49 Years	255 (12) 5.0%	164 (6) 3.8%	2 (0) 0%	396 (18) 4.5%
Age - 50-59 Years	321 (17) 5.2%	372 (23) 6.4%	9 (0) 0%	671 (40) 5.8%
Age - 60-69 Years	560 (32) 5.4%	664 (38) 5.3%	12 (0) 0%	1184 (70) 5.3%
Age - 70-79 Years	514 (41) 7.9%	506 (36) 7.1%	5 (0) 0%	1003 (77) 7.5%
Age - 80+ Years	265 (30) 11.2%	167 (26) 14.3%	6 (0) 0%	425 (56) 12.2%
Age Unknown	156 (10) 6.7%	124 (6) 5.4%	48 (1) 2.1%	308 (17) 5.5%
Grand Total	**2293 (152) 6.6%**	**2117 (140) 6.5%**	**85 (1) 1.2%**	**4495 (293) 6.5%**

N, Number of cases

Among 293 cases with fatal outcomes, medical history information was available for 188 cases. Risk/confounding factors included the following: hypertension (55), diabetes mellitus (37), obesity (25), asthma (18), pulmonary embolism (16), dementia (15), myocardial ischaemia (12), chronic obstructive pulmonary disease (11), anxiety (10), osteoarthritis (10), bone fractures (10), tobacco user (10), cardiac failure (9), hypercholesterolaemia (9), deep vein thrombosis (8), arteriosclerosis (7), rectal cancer (6), asthenia (5), dyspnoea (5), hyperlipidaemia (5), rheumatoid arthritis (5), suspected covid-19 (5), varicose vein (5), myocardial infarction (5), alcoholism (5), immobile (4), radiotherapy (4), cerebrovascular accident (4), dyspnoea exertional (4), immunodeficiency (4), spinal fracture (4), ex-tobacco user (4), lower respiratory tract infection (4), arteriosclerosis coronary artery (4), atrial fibrillation (4), cardiac arrest (4), chronic kidney disease (4), thyroid disorders (3), hepatic steatosis (3), breast cancer (3), chemotherapy (3), knee arthroplasty (3), diverticulum (3), covid-19 (3), transient ischaemic attack (3), lung neoplasm malignant (3), atrioventricular block (2), atrial septal defect (2), Parkinson's disease (2), arthralgia (2), pneumonia (2), fall (2), gastrectomy (2), cellulitis (2), colostomy (2), goitre (2), neoplasm (2), gout (2), basal cell carcinoma (2), peripheral venous disease (2), chest pain (2), sleep apnoea syndrome (2), thrombocytopenia (2), malignant melanoma (2), aortic aneurysm (2), gastric bypass (2), pancreatic carcinoma metastatic (2), hepatic cirrhosis (2), cerebral palsy (2),

irritable bowel syndrome (2), prosthetic cardiac valve failure (1), orthopaedic procedure (1), colon cancer (1), small intestinal obstruction (1), colorectal cancer (1), cerebral haemorrhage (1), Basedow's disease (1), renal failure (1), congestive cardiomyopathy (1), metabolic syndrome (1), cor pulmonale (1), neurofibromatosis (1), coronary artery bypass (1), coronary artery disease (1), adrenogenital syndrome (1), aortic dilatation (1), craniopharyngioma (1), throat cancer (1), craniotomy (1), tuberculosis (1), cerebral haematoma (1), cerebral haemorrhage (1), deficiency anaemia (1), cerebral thrombosis (1), arteritis (1), phlebitis superficial (1), pregnancy (1), pulmonary atypical adenomatous hyperplasia (1), sickle cell disease (1), diabetic nephropathy (1), dilatation atrial (1), squamous cell carcinoma of the cervix (1), disability (1), transsphenoidal surgery (1), bronchiectasis (1), metastatic neoplasm (1), bronchitis viral (1), cerebral haematoma (1), aneurysm (1), emphysema (1), cerebrospinal fluid reservoir placement (1), exposure to chemical pollution (1), cachexia (1), plasma cell myeloma (1), prostate cancer (1), pulmonary hypertension (1), Rett syndrome (1), bladder cancer (1), splenectomy (1), steroid therapy (1), gastroduodenal ulcer (1), gastrointestinal carcinoma (1), t-cell lymphoma (1), cardiac pacemaker insertion (1), traumatic lung injury (1), cardiac valve prosthesis user (1), haemangioma of liver (1), metastases to liver (1), cerebral atrophy (1), haemorrhoids (1), Morton's neuralgia (1), hemiplegia (1), hepatic cancer metastatic (1), neoplasm malignant (1), nephrosclerosis (1), hepatic neoplasm (1), arteriosclerosis coronary artery (1), non-alcoholic fatty liver disease (1), angina pectoris (1), hepatitis (1), obesity cardiomyopathy (1), herpes zoster (1), hiv test positive (1), pancreatic carcinoma (1), hydrocephalus (1), pancreatic disorder (1), peptic ulcer (1), pneumonectomy (1), hypopituitarism (1), cardiomegaly (1), pulmonary tuberculosis (1), pulmonary endarterectomy (1), urinary tract infection (1), cardioversion (1), renal hypertrophy (1), ventricular extrasystoles (1), ventriculo-peritoneal shunt (1), right ventricular hypertrophy (1), carotid artery stenosis (1), sepsis (1), ischaemic cardiomyopathy (1), sinus tachycardia (1), ischaemic stroke (1), knee operation (1), Korsakoff's syndrome (1), large intestine operation (1), squamous cell carcinoma of skin (1), large intestine polyp (1), steroid therapy (1), left ventricular hypertrophy (1), limb operation (1), tachycardia (1), thrombectomy (1), thrombosis (1), transplant (1), trisomy 2 (1), autoimmune disorder (1), inflammation (1), ventricular hypertrophy (1), ventriculo-pleural shunt (1), interstitial lung disease (1), and hypertensive heart disease (1).

One case may have more than multiple risk/confounding factors.

The reported PTs with a fatal outcome in the 4316 cases of PE without thrombocytopenia in order of frequency (>6) were Pulmonary embolism (249), Deep vein thrombosis (47), Cardiac arrest (16), Dyspnoea (15), Thrombosis (13), and Pneumonia (8).

Outcomes in the remaining 4202 non-fatal case reports of PE without thrombocytopenia were: Not Recovered 1352 (30.1%), Recovered 404 (8.9%), Recovering 1673 (37.2%), Recovered With Sequelae 121 (2.7%), and Unknown/missing 652 (14.5%).

The time to onset from the administration of vaccine to the onset of the PE event was available in 2586 (57.5%) case reports. The time to onset from the administration of vaccine to the event

onset was 0-7 days in 975 (21.7%), 8-14 days in 503 (11.2%), 15-21 days in 301 (6.7%), 22-28 days in 197 (4.4%), and greater than 28 days in 610 (13.6%) of cases. The time to onset ranged between 0-278 days with a median of 12 days.

There was available information on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 2371 (52.7%) of the 4495 cases.

These confounding conditions were medical histories of: hypertension (551), pulmonary embolism (284), cases with past drug use of heparin suggesting history of thrombotic events (198), diabetes mellitus (191), obesity (187), asthma (184), suspected covid-19 (142), deep vein thrombosis (114), depression (97), dyspnoea (97), chronic obstructive pulmonary disease (94), tobacco user (86), chest pain (82), osteoarthritis (77), hypothyroidism (73), hypercholesterolaemia (72), breast cancer (70), dyslipidaemia (68), sleep apnoea syndrome (57), overweight (56), rheumatoid arthritis (55), covid-19 (49), steroid therapy (47), myocardial ischaemia (42), ex-tobacco user (41), myocardial infarction (40), pneumonia (39), prostate cancer (34), anxiety (32), hyperlipidaemia (31), hypersensitivity (30), thrombosis (28), chronic kidney disease (27), immunodeficiency (26), migraine (26), neoplasm (26), cerebrovascular accident (26), atrial fibrillation (25), neoplasm malignant (25), cough (25), surgery (25), osteoporosis (24), gout (24), peripheral venous disease (20), lung neoplasm malignant (19), dementia (19), back pain (19), fibromyalgia (16), psoriasis (16), pregnancy (16), fall (15), epilepsy (15), hip arthroplasty (15), knee arthroplasty (14), bronchiectasis (14), nephrectomy (14), thyroidectomy (13), arteriosclerosis (13), phlebitis (13), embolism (13), immobile (13), mixed anxiety and depressive disorder (13), radiotherapy (13), sciatica (12), varicose vein (12), cardiac failure (12), coronary artery disease (11), arrhythmia (11), chemotherapy (11), malignant melanoma (11), lower respiratory tract infection (11), superficial vein thrombosis (10), goitre (10), splenectomy (10), atrial fibrillation (10), palpitations (10), transient ischaemic hyperuricaemia (11), arthritis (11), attack (9), angina pectoris (9), thrombophlebitis (9), emphysema (9), sepsis (8), spinal pain (8), Parkinson's disease (8), hospitalisation (8), fatigue (8), urinary tract infection (8), and varicose vein operation (8).

Concomitant confounding medications included prednisone (69), sertraline (44), prednisolone (40), citalopram (35), amitriptyline (34), mirtazapine (24), methotrexate (20), venlafaxine (17), fluoxetine (15), olanzapine (13), estradiol (12), duloxetine (11), escitalopram (9), dexamethasone (7), mometasone (5), contraceptives (4), quinine (3), hydrocortisone (3), and estrogen (2).

Additionally, possible confounding concomitant events included the following: deep vein thrombosis (801), fibrin d dimer increased (214), thrombosis (201), pain in extremity (185), pneumonia (121), embolism (100), asthenia (85), myalgia (82), arthralgia (62), back pain (61), vomiting (46), heavy menstrual bleeding (46), haemorrhage (52), atrial fibrillation (37), diarrhoea (35), covid-19 (34), influenza like illness (30), venous thrombosis (28), hypertension (28), cardiac disorder (27), cardiac failure (25), venous thrombosis limb (25), lower respiratory

tract infection (21), cerebrovascular accident (21), superficial vein thrombosis (20), thrombophlebitis (20), coagulopathy (19), hypotension (18), phlebitis (16), myocardial infarction (14), pneumonitis (13), sepsis (11), infection (11), erythema (11), fall (11), asthma (11), cardiomegaly (11), urinary tract infection (10), renal infarct (10), ischaemic stroke (10), and cerebral infarction (10).

A single case may have more than one risk factor.

PE without thrombocytopenia events after 2nd dose of the Vaccine

There were 296 case reports in individuals who were reported to have received 2 doses of vaccine and the PE event occurred post 2nd dose. Age was reported for 277 case reports. In 233 (84.1%) of the case reports were age was reported and the event occurred post 2nd dose, the vaccinee was >50 years. Of the 296 reports, 145 (49.0%) were in females, 149 (50.3%) in males, and gender was unknown for 2 (0.7%) reports. TTO after 2nd dose was reported as 0-7 days in 97 (27.3%) cases, 8-14 days in 47 (15.8%) cases, 15-21 days in 39 (15.4%) cases, 22-28 days in 24 (11.9%) cases, and >28 days in 89 (29.6%) cases.

Among the total of 296 cases who had PE events after the 2nd dose, medical history was available for 242 (81.8%) cases. The most frequently reported (≥3) risk/confounding factors were: hypertension (35), cases had past use of heparin suggesting history of thrombotic/embolic events (32), tobacco user (15), depression (12), pulmonary embolism (12), chest pain (10), deep vein thrombosis (10), suspected covid-19 (10), obesity (10), dyspnoea (9), diabetes mellitus (9), asthma (8), covid-19 (7), chronic obstructive pulmonary disease (7), hypercholesterolaemia (6), steroid therapy (5), breast cancer (5), pneumonia (5), rheumatoid arthritis (5), cerebrovascular accident (5), osteoarthritis (4), hypothyroidism (4), neoplasm malignant (4), factor v leiden mutation (3), pregnancy (3), dyslipidaemia (3), sleep apnoea syndrome (3), palpitations (3), surgery (3), myocardial ischaemia (3), neoplasm (3), head injury (3), and cardiac failure (3).

Concomitant confounding drugs included the following (frequency ≥2): prednisolone (5), sertraline (5), citalopram (4), carbamazepine (3), venlafaxine (3), mirtazapine (2), and olanzapine (2).

Additionally, possible confounding concomitant events included the following (frequency ≥2): pneumonia (11), haemorrhage (10), cardiac disorder (4), lower respiratory tract infection (4), covid-19 (3), cardiac arrest (2), angina pectoris (2), cardiac disorder (2), peripheral ischaemia (2), cardiomegaly (2), and cerebral infarction (2).

A single case may have more than one risk factor.

There were 14 deaths reported out of 296 case reports. Detail of these 14 fatal outcomes are provided in Table 63 below. Age of the 14 vaccinees with a fatal outcome ranged from 33 to 79 with a median of 64 years.

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	Not recovered	Pulmonary embolism	9	Died	PPD		PPD of the patient as well as multiple comorbidities including asthma, angina pectoris, hypercholesterolaemia, NIDDM pacemaker for MOBITZ 1 AV block, type 2 diabetes mellitus, diverticulosis, and hypertension could be contributory.

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
									PPD	
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	6	Died	UNK		PPD is a risk factor for the fatal event. Confounded by polypharmacy.

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	85		Pulmonary embolism	0	Died	PPD	UNK	Risk factors as type 2 diabetes mellitus, hypertension arterial, PPD could be considered as contributory factors for the events.

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	5	Died	UNK	UNK	Pulmonary embolism and other reported events of dyspnoea, chronic obstructive pulmonary disease could be in association with each other.

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	23	Died	PPD		Concomitant event of deep vein thrombosis could be a confounding factor for the event pulmonary embolism. Suspected COVID-19 could be a risk factor for the fatal event Pulmonary embolism. Concomitant medication of PPD PPD

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	6	Died	PPD	UNK	The reported history of PPD could be a risk factor for the event of pulmonary embolism.
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	5	Died		UNK	PPD of the patient, as well as medical history of PPD and breast cancer, could be risk factors for the event.
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	1	Died	UNK	UNK	UNK

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	18	Died	PPD		Concomitant event of Cardiac arrest and Deep vein thrombosis could be a contributing risk factor of Pulmonary embolism. Relevant medication history of PPD indicates thromboembolic event in past which could be confounding factor of Pulmonary embolism

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	14	Died	PPD	UNK	PPD of the patient could be a predisposing factor. Medical history of phlebitis, Alzheimer's disease, sleep apnoea syndromes, breast cyst, non-insulin-dependent diabetes mellitus, gastroduodenal ulcer, Basedow's disease and hypertension arterial could be contributory risk factors for the event.

PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	48	Died	PPD		Concomitant reported events of Pulmonary embolism, Deep vein thrombosis, Platelet count increased, Thrombosis and Arterial thrombosis could have been in association with each other. Pulmonary embolism could also be in association with reported events of Pyrexia, Pneumonia, Respiratory failure and Cardio-respiratory arrest.
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	124	Died	PPD	UNK	PPD and medical history of

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
										oily tumor could be considered as risk factors for the event and for the fatal outcome.
PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	31	Died	UNK	UNK	Reported events of Deep vein thrombosis, Pulmonary embolism and Fibrin D dimer increased could be in association with each other.

PPD	PPD	Pulmonary embolism	UNK	UNK	Pulmonary embolism	2	Died	Rheumatoid arthritis	UNK	The case is not medically confirmed. Reported events of Pulmonary embolism, Cough, Lower respiratory tract infection and Dyspnoea could be in association with each other. PPD could be a possible contributory risk factor for the event Pulmonary embolism. Relevant medical history of rheumatoid arthritis could confound to the

Table 63 Patients with fatal PE events after Dose 1 and Dose 2 (n = 14) with COVID-19 VACCINE ASTRAZENECA during the reporting period (29 June 2021 – 28 December 2021)

Case ID/ Country	Sex/ Age	Events after first dose	TTO (days)	Outcome	Events after second dose	TTO (days)	Outcome	Medical history	Concomitant medications	Confounding factors
										event Pulmonary embolism.

UNK, Unknown; TTO, Time to Onset

There was 1 case (PPD) where a PE event was reported to have occurred after both 1st and 2nd dose. In this case, a PPD patient of unknown age was reported to have experienced pulmonary thrombosis after both 1st and 2nd dose of vaccine. TTO was not reported and there was no information on medical history, concurrent diseases or concomitant medications. Outcome of the event was not reported.

PE without thrombocytopenia events after 3rd dose of the vaccine

There was 1 case (PPD) where a PE event was reported to have occurred after 3rd dose of the vaccine. A PPD patient of unknown age had Pulmonary embolism 5 days after receiving 3rd dose of vaccine. Reported medical history of malignant neoplasm could be contributory to the event. No other information on medical history or concomitant medications were reported. At the time of reporting the patient was reported as recovering.

Observed versus Expected Analysis

The observed versus expected analyses for all cases of PE without thrombocytopenia are carried out using incidence rates from Truven Market Scan (2019). These analyses are presented with 14, 28 and 42 risk window (this is the same risk window used for other thromboembolic events) for all global reports and stratified by age in the EEA and UK regions, and by age and gender in the UK. All stratifications are also included including cases with an unknown time to onset, as a conservative approach.

The O/E analysis results for PE without thrombocytopenia showed observed cases to be significantly less or less than expected for all stratifications (Table 64).

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	14	159.84	291626957	2141	17867.34	0.12 (0.11 - 0.13)	Observed significantly < expected
Overall (Global) with Unk TTO	14	159.84	291626957	2927	17867.34	0.16 (0.16 - 0.17)	Observed significantly < expected
Overall (Global)	28	159.84	291626957	2828	35734.68	0.08 (0.08 - 0.08)	Observed significantly < expected
Overall (Global) with Unk TTO	28	159.84	291626957	3614	35734.68	0.1 (0.1 - 0.1)	Observed significantly < expected
Overall (Global)	42	159.84	291626957	3213	53602.02	0.06 (0.06 - 0.06)	Observed significantly < expected
Overall (Global) with Unk TTO	42	159.84	291626957	3999	53602.02	0.07 (0.07 - 0.08)	Observed significantly < expected
Female 18 to 29 UK	14	49.68	1339334	23	25.5	0.9 (0.57 - 1.35)	Observed significantly < expected
Female 30 to 39 UK	14	91.29	2096348	39	73.36	0.53 (0.38 - 0.73)	Observed significantly < expected
Female 40 to 49 UK	14	149.98	4974220	72	285.96	0.25 (0.2 - 0.32)	Observed significantly < expected
Female 50 to 59 UK	14	165.36	6319086	75	400.53	0.19 (0.15 - 0.23)	Observed significantly < expected
Female 60 to 69 UK	14	248.36	4859019	66	462.57	0.14 (0.11 - 0.18)	Observed significantly < expected
Female 70 to 79 UK	14	565.32	3562147	65	771.89	0.08 (0.06 - 0.11)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female over 80 UK	14	832.38	1721795	34	549.35	0.06 (0.04 - 0.09)	Observed significantly < expected
Male 18 to 29 UK	14	23.68	986375	5	8.95	0.56 (0.18 - 1.3)	Observed < expected
Male 30 to 39 UK	14	53.26	1582807	24	32.31	0.74 (0.48 - 1.11)	Observed < expected
Male 40 to 49 UK	14	107.38	5220928	50	214.89	0.23 (0.17 - 0.31)	Observed significantly < expected
Male 50 to 59 UK	14	206.22	6957211	75	549.94	0.14 (0.11 - 0.17)	Observed significantly < expected
Male 60 to 69 UK	14	322.95	4966917	73	614.85	0.12 (0.09 - 0.157)	Observed significantly < expected
Male 70 to 79 UK	14	606.06	3223317	59	748.8	0.08 (0.06 - 0.1)	Observed significantly < expected
Male over 80 UK	14	790.79	1042292	12	315.93	0.04 (0.02 - 0.07)	Observed significantly < expected
Female 18 to 29 UK	28	49.68	1339334	31	51.01	0.61 (0.41 - 0.86)	Observed significantly < expected
Female 30 to 39 UK	28	91.29	2096348	47	146.71	0.32 (0.24 - 0.43)	Observed significantly < expected
Female 40 to 49 UK	28	149.98	4974220	90	571.92	0.16 (0.13 - 0.19)	Observed significantly < expected
Female 50 to 59 UK	28	165.36	6319086	94	801.05	0.12 (0.09 - 0.14)	Observed significantly < expected
Female 60 to 69 UK	28	248.36	4859019	94	925.14	0.1 (0.08 - 0.12)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 70 to 79 UK	28	565.32	3562147	89	1543.77	0.06 (0.05 - 0.07)	Observed significantly < expected
Female over 80 UK	28	832.38	1721795	45	1098.7	0.04 (0.03 - 0.05)	Observed significantly < expected
Male 18 to 29 UK	28	23.68	986375	8	17.91	0.45 (0.19 - 0.88)	Observed significantly < expected
Male 30 to 39 UK	28	53.26	1582807	30	64.63	0.46 (0.31 - 0.66)	Observed significantly < expected
Male 40 to 49 UK	28	107.38	5220928	64	429.78	0.15 (0.11 - 0.19)	Observed significantly < expected
Male 50 to 59 UK	28	206.22	6957211	97	1099.87	0.09 (0.07- 0.11)	Observed significantly < expected
Male 60 to 69 UK	28	322.95	4966917	93	1229.7	0.08 (0.06 - 0.09)	Observed significantly < expected
Male 70 to 79 UK	28	606.06	3223317	76	1497.6	0.05 (0.04 - 0.06)	Observed significantly < expected
Male over 80 UK	28	790.79	1042292	19	631.87	0.03 (0.02 - 0.05)	Observed significantly < expected
Female 18 to 29 UK	42	49.68	1339334	38	76.51	0.5 (0.35 - 0.68)	Observed significantly < expected
Female 30 to 39 UK	42	91.29	2096348	50	220.07	0.23 (0.17 - 0.3)	Observed significantly < expected
Female 40 to 49 UK	42	149.98	4974220	107	857.88	0.12 (0.1 - 0.15)	Observed significantly < expected
Female 50 to 59 UK	42	165.36	6319086	101	1201.58	0.08 (0.07 - 0.1)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 60 to 69 UK	42	248.36	4859019	104	1387.71	0.07 (0.06 - 0.09)	Observed significantly < expected
Female 70 to 79 UK	42	565.32	3562147	104	2315.66	0.04 (0.04 - 0.05)	Observed significantly < expected
Female over 80 UK	42	832.38	1721795	48	1648.05	0.03 (0.02 - 0.04)	Observed significantly < expected
Male 18 to 29 UK	42	23.68	986375	10	26.86	0.37 (0.18 - 0.68)	Observed significantly < expected
Male 30 to 39 UK	42	53.26	1582807	34	96.94	0.35 (0.24 - 0.49)	Observed significantly < expected
Male 40 to 49 UK	42	107.38	5220928	74	644.67	0.11 (0.09 - 0.14)	Observed significantly < expected
Male 50 to 59 UK	42	206.22	6957211	110	1649.81	0.07 (0.05 - 0.08)	Observed significantly < expected
Male 60 to 69 UK	42	322.95	4966917	111	1844.55	0.06 (0.05 - 0.07)	Observed significantly < expected
Male 70 to 79 UK	42	606.06	3223317	90	2246.4	0.04 (0.03 - 0.05)	Observed significantly < expected
Male over 80 UK	42	790.79	1042292	20	947.8	0.02 (0.01 - 0.03)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	14	49.68	1339334	25	25.5	0.98 (0.63 - 1.45)	Observed < expected
Female 30 to 39 UK with Unk TTO	14	91.29	2096348	50	73.36	0.68 (0.51 - 0.9)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 40 to 49 UK with Unk TTO	14	149.98	4974220	90	285.96	0.31 (0.25 - 0.39)	Observed significantly < expected
Female 50 to 59 UK with Unk TTO	14	165.36	6319086	92	400.53	0.23 (0.19 - 0.28)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	14	248.36	4859019	80	462.57	0.17 (0.14 - 0.22)	Observed significantly < expected
Female 70 to 79 UK with Unk TTO	14	565.32	3562147	77	771.89	0.1 (0.08 - 0.12)	Observed significantly < expected
Female over 80 UK with Unk TTO	14	832.38	1721795	45	549.35	0.08 (0.06 - 0.11)	Observed significantly < expected
Male 18 to 29 UK with Unk TTO	14	23.68	986375	5	8.95	0.56 (0.18 - 1.3)	Observed < expected
Male 30 to 39 UK with Unk TTO	14	53.26	1582807	28	32.31	0.87 (0.58 - 1.25)	Observed < expected
Male 40 to 49 UK with Unk TTO	14	107.38	5220928	60	214.89	0.28 (0.21 - 0.36)	Observed significantly < expected
Male 50 to 59 UK with Unk TTO	14	206.22	6957211	111	549.94	0.2 (0.17 - 0.24)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	14	322.95	4966917	89	614.85	0.14 (0.12 - 0.18)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	14	606.06	3223317	80	748.8	0.11 (0.08 - 0.13)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male over 80 UK with Unk TTO	14	790.79	1042292	20	315.93	0.06 (0.04 - 0.1)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	28	49.68	1339334	33	51.01	0.65 (0.45 - 0.91)	Observed significantly < expected
Female 30 to 39 UK with Unk TTO	28	91.29	2096348	58	146.71	0.4 (0.3 - 0.51)	Observed significantly < expected
Female 40 to 49 UK with Unk TTO	28	149.98	4974220	108	571.92	0.19 (0.15 - 0.23)	Observed significantly < expected
Female 50 to 59 UK with Unk TTO	28	165.36	6319086	111	801.05	0.14 (0.11 - 0.17)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	28	248.36	4859019	108	925.14	0.12 (0.1 - 0.14)	Observed significantly < expected
Female 70 to 79 UK with Unk TTO	28	565.32	3562147	101	1543.77	0.07 (0.05 - 0.08)	Observed significantly < expected
Female over 80 UK with Unk TTO	28	832.38	1721795	56	1098.7	0.05 (0.04 - 0.07)	Observed significantly < expected
Male 18 to 29 UK with Unk TTO	28	23.68	986375	8	17.91	0.45 (0.19 - 0.88)	Observed significantly < expected
Male 30 to 39 UK with Unk TTO	28	53.26	1582807	34	64.63	0.53 (0.36 - 0.74)	Observed significantly < expected
Male 40 to 49 UK with Unk TTO	28	107.38	5220928	74	429.78	0.17 (0.14 - 0.22)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 50 to 59 UK with Unk TTO	28	206.22	6957211	133	1099.87	0.12 (0.1 - 0.14)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	28	322.95	4966917	109	1229.7	0.09 (0.07 - 0.11)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	28	606.06	3223317	97	1497.6	0.06 (0.05 - 0.08)	Observed significantly < expected
Male over 80 UK with Unk TTO	28	790.79	1042292	27	631.87	0.04 (0.03 - 0.06)	Observed significantly < expected
Female 18 to 29 UK with Unk TTO	42	49.68	1339334	40	76.51	0.52 (0.37 - 0.71)	Observed significantly < expected
Female 30 to 39 UK with Unk TTO	42	91.29	2096348	61	220.07	0.28 (0.21 - 0.36)	Observed significantly < expected
Female 40 to 49 UK with Unk TTO	42	149.98	4974220	125	857.88	0.15 (0.12 - 0.17)	Observed significantly < expected
Female 50 to 59 UK with Unk TTO	42	165.36	6319086	118	1201.58	0.1 (0.08 - 0.12)	Observed significantly < expected
Female 60 to 69 UK with Unk TTO	42	248.36	4859019	118	1387.71	0.09 (0.07 - 0.1)	Observed significantly < expected
Female 70 to 79 UK with Unk TTO	42	565.32	3562147	116	2315.66	0.05 (0.04 - 0.06)	Observed significantly < expected
Female over 80 UK with Unk TTO	42	832.38	1721795	59	1648.05	0.04 (0.03 - 0.05)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18 to 29 UK with Unk TTO	42	23.68	986375	10	26.86	0.37 (0.18 - 0.68)	Observed significantly < expected
Male 30 to 39 UK with Unk TTO	42	53.26	1582807	38	96.94	0.39 (0.28 - 0.54)	Observed significantly < expected
Male 40 to 49 UK with Unk TTO	42	107.38	5220928	84	644.67	0.13 (0.1 - 0.16)	Observed significantly < expected
Male 50 to 59 UK with Unk TTO	42	206.22	6957211	146	1649.81	0.09 (0.07 - 0.1)	Observed significantly < expected
Male 60 to 69 UK with Unk TTO	42	322.95	4966917	127	1844.55	0.07 (0.06 - 0.08)	Observed significantly < expected
Male 70 to 79 UK with Unk TTO	42	606.06	3223317	111	2246.4	0.05 (0.04 - 0.06)	Observed significantly < expected
Male over 80 UK with Unk TTO	42	790.79	1042292	28	947.8	0.03 (0.02 - 0.04)	Observed significantly < expected
All 18-49 EEA/UK	14	81.75	27716022	358	868.49	0.41 (0.37 - 0.46)	Observed significantly < expected
All 18-49 EEA/UK with Unk TTO	14	81.75	27716022	426	868.49	0.49 (0.45 - 0.54)	Observed significantly < expected
All 50-59 EEA/UK	14	184.66	19552392	304	1383.95	0.22 (0.2 - 0.25)	Observed significantly < expected
All 50-59 EEA/UK with Unk TTO	14	184.66	19552392	372	1383.95	0.27 (0.24 - 0.3)	Observed significantly < expected
All 60-69 EEA/UK	14	283.69	28510714	541	3100.27	0.17 (0.16 - 0.19)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 60-69 EEA/UK with Unk TTO	14	283.69	28510714	592	3100.27	0.19 (0.18 - 0.21)	Observed significantly < expected
All 70-79 EEA/UK	14	584.02	14795684	380	3312.15	0.11 (0.1 - 0.13)	Observed significantly < expected
All 70-79 EEA/UK with Unk TTO	14	584.02	14795684	439	3312.15	0.13 (0.12 - 0.15)	Observed significantly < expected
All over 80 EEA/UK	14	815.22	3858135	122	1205.59	0.1 (0.08 - 0.12)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	14	815.22	3858135	148	1205.59	0.12 (0.1 - 0.14)	Observed significantly < expected
All 18-49 EEA/UK	28	81.75	27716022	450	1736.98	0.26 (0.24 - 0.28)	Observed significantly < expected
All 18-49 EEA/UK with Unk TTO	28	81.75	27716022	518	1736.98	0.3 (0.27 – 0.33)	Observed significantly < expected
All 50-59 EEA/UK	28	184.66	19552392	397	2767.89	0.14 (0.13 - 0.16)	Observed significantly < expected
All 50-59 EEA/UK with Unk TTO	28	184.66	19552392	465	2767.89	0.17 (0.15 - 0.18)	Observed significantly < expected
All 60-69 EEA/UK	28	283.69	28510714	707	6200.53	0.11 (0.11 - 0.12)	Observed significantly < expected
All 60-69 EEA/UK with Unk TTO	28	283.69	28510714	758	6200.53	0.12 (0.11 - 0.13)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 70-79 EEA/UK	28	584.02	14795684	511	6624.29	0.09 (0.08 - 0.09)	Observed significantly < expected
All 70-79 EEA/UK with Unk TTO	28	584.02	14795684	570	6624.29	0.09 (0.08 - 0.09)	Observed significantly < expected
All over 80 EEA/UK	28	815.22	3858135	169	2411.18	0.07 (0.06 - 0.08)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	28	815.22	3858135	195	2411.18	0.08 (0.07 - 0.09)	Observed significantly < expected
All 18-49 EEA/UK	42	81.75	27716022	519	2605.47	0.2 (0.18 - 0.22)	Observed significantly < expected
All 18-49 EEA/UK with Unk TTO	42	81.75	27716022	587	2605.47	0.23 (0.21 - 0.24)	Observed significantly < expected
All 50-59 EEA/UK	42	184.66	19552392	445	4151.84	0.11 (0.1 - 0.12)	Observed significantly < expected
All 50-59 EEA/UK with Unk TTO	42	184.66	19552392	513	4151.84	0.12 (0.11 - 0.13)	Observed significantly < expected
All 60-69 EEA/UK	42	283.69	28510714	814	9300.8	0.09 (0.09 - 0.1)	Observed significantly < expected
All 60-69 EEA/UK with Unk TTO	42	283.69	28510714	865	9300.8	0.09 (0.08 - 0.09)	Observed significantly < expected
All 70-79 EEA/UK	42	584.02	14795684	582	9936.44	0.06 (0.05 - 0.06)	Observed significantly < expected

Table 64 Observed versus expected analyses for PE without thrombocytopenia

Age group/ Gender	Risk window	IR [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All 70-79 EEA/UK with Unk TTO	42	584.02	14795684	641	9936.44	0.06 (0.06 - 0.07)	Observed significantly < expected
All over 80 EEA/UK	42	815.22	3858135	187	3616.76	0.05 (0.04 - 0.06)	Observed significantly < expected
All over 80 EEA/UK with Unk TTO	42	815.22	3858135	213	3616.76	0.06 (0.05 - 0.07)	Observed significantly < expected

[a] IBM MarketScan CCAE/MDCR 2008 thru 2020Q1

Exposure until 28 December 2021,

CI, Confidence Interval; E, Expected; IR, Incidence Rate; O, Observed; TTO, Time to onset.

The results of the observed versus expected analyses concluded that the observed cases of PE without thrombocytopenia were significantly less than expected in the background population overall and across different sexes, age groups, and regions.

Literature

A cumulative search through 28 December 2021 of the PubMed and Embase databases were undertaken to identify any new articles discussing PE without thrombocytopenia with COVID-19 vaccine since the previous review in the 8th SSR (review period: 01 October 2021 – 30 November 2021).

There were no new articles relevant to this safety topic identified. In addition, there were no articles identified discussing a possible mechanism of action between development of PE with COVID-19 VACCINE ASTRAZENCA.

Summary

In 18-49 age group, 62.7% of cases occurred in females. Of the 4495 cases, there were 296 (6.6%) case reports in individuals who were reported to have received 2 doses of vaccine and the event occurred post 2nd dose and 1 case report were the individual had received 3 doses. Thirty-three fatal cases (11.3%) out of all 293 fatal cases occurred in 18-49 age group. There were 152 (52.1%) fatal reports in females and 140 (47.9%) fatal reports in males. All case reports were serious. The time to onset from the administration of vaccine to the onset of PE was within 28

days in 76.4% of the case reports that reported TTO. Underlying cause/ confounding factors were noted in 52.7% of cases.

These confounding conditions were medical histories of: hypertension, pulmonary embolism, previous thrombotic/embolic events, diabetes mellitus, asthma, covid-19, tobacco, hypothyroidism, hypercholesterolaemia/dyslipidaemia/ hyperlipidaemia, cancers, overweight/obesity, autoimmune disorders, steroid therapy, cardiac diseases, arrythmias, respiratory system diseases, renal disorders, immunodeficiency, sepsis/infections, cerebrovascular accident, surgery, gout, peripheral venous diseases, pregnancy, fall, arthroplasties, arteriosclerosis, immobile, radiotherapy, varicose vein, and chemotherapy.

There were no imbalances in rates of PE between active vaccine and control group within the clinical trials for AZD1222.

The results of the observed versus expected analyses concluded that the observed cases of PE without thrombocytopenia were significantly less than expected in the background population overall and across different sexes, age groups, and regions.

No potential mechanisms of action regarding PE without thrombocytopenia with COVID-19 VACCINE have been identified.

Conclusion

From this updated review, AstraZeneca did not find evidence of a new or emerging signal regarding PE without thrombocytopenia and COVID-19 VACCINE ASTRAZENECA. No changes to the CDS or RMP are recommended. PE without thrombocytopenia will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

15.2.16 Photophobia

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021:

"The MAH is requested to comment on the signal from WHO-UMC on Photophobia and to provide a cumulative review of cases reported with Vaxzevria. A discussion on the need to update the PI should be included."

AstraZeneca's response to this request is provided below.

Review of Cases

A cumulative search of the AstraZeneca global safety database through 28 December 2021 using the PT: Photophobia (MedDRA v24.1) with COVID-19 VACCINE ASTRAZENECA was conducted. The search retrieved 2069 events of Photophobia in 2069 cases from the following sources - spontaneous (2027 cases, 98%), non-interventional / post-market study (36 cases, 1.7%) and literature (6 cases, 0.3%).

Out of the 2069 cases, 347 cases (17%) were medically confirmed. Out of the 2069 events of Photophobia, 1055 (51%) were reported as serious due to: death (4), AE was considered life-threatening event (28), AE reportedly resulted in hospitalization (124), reportedly resulted in disability (193), or were reportedly considered as medically important (706). The remaining 1014 (49%) cases were reported as non-serious.

Age was reported in 1911 of the 2069 reports of photophobia with a median age of 43 years. The gender distribution as reported in 2006 cases was 80% females (1613 cases) and 20% males (393 cases). The TTO of vaccine administration to event of photophobia was reported in 1492 AEs (72.1%), out of which 92% (n=1371) were reported in ≤ 7 days and 88% (n=1313) in ≤ 3 days as shown in Table 65. No particular chronology trend was seen in the remaining few AEs reported with a latency beyond 7 days.

The AE outcome was recovered / recovering in 738 AEs (56%), recovered with sequelae in 25 AEs (1%), not recovered in 564 AEs (27%) and fatal in 4 AEs (<0.2%). The AE outcome was unknown in 309 AEs (15%). The duration of AE was reported in 451 AEs with a range of 30 minutes to 122 days and mean and median duration was 3.8 days and 2 days respectively. The duration of the AE was reported ≤ 7 days in 413 AEs (91.6%) and in ≤ 3 days in 362 AEs (80.3%).

The relevant event occurred after dose 1 for the majority of cases, dose 2 for only two cases (PPD) and both doses for only one case (PPD). In one case PPD , the patient had received both doses of the vaccine, however the AE occurrence was reported only on first dose and not on second dose.

The latency of AE to vaccine administration was reported in 1492 AEs (72.1%), out of which 92% (n=1371) were reported in ≤ 7 days and 88% (n=1313) in ≤ 3 days as shown in Table 65. No particular chronology trend was seen in the remaining few AEs reported with a latency beyond 7 days. The duration of AE was reported in 451 AEs with a range of 30 minutes to 122 days and mean and median duration on 3.8 days and 2 days respectively. The duration of the AE was reported ≤ 7 days in 413 AEs (91.6%) and in ≤ 3 days in 362 AEs (80.3%).

Table 65 Distribution of TTO of Events of Photophobia from administration of COVID-19 VACCINE ASTRAZENECA, cumulatively through 28 December 2021

Time First Dose To AE Onset	Number of PTs	Percentage
00 Under 1 day	600	28.3
01 day	610	28.8
02 days	67	3.2
03 days	36	1.7
04 days	16	0.8
05 days	13	0.6
06 days	13	0.6
07 days	16	0.8
08 days	12	0.6
09 days	10	0.5
10 to 15 days	30	1.4
16 to 20 days	8	0.4
21 to 30 days	18	0.8
31 to 40 days	6	0.3
41 to 60 days	8	0.4
61 to 80 days	11	0.5
81 to 100 days	9	0.4
Over 100 to 200 days	4	0.2
Over 1 year	1	0.1
Erroneous*	4	0.1
Undefined (missing)	629	29.7

AE, Adverse Event; PTs, Preferred Terms; TTO Time to Onset.

From the total number of cases retrieved in the AstraZeneca Safety database, only approximately 1% (20 AEs out of 2069) reported photophobia as a single AE [majority were non-serious (17 AEs, 85%) or with limited information on seriousness criteria (remaining 3 regulatory cases), majority with known outcome as favourable (12 AEs out of 17, 71%) with no fatal or life-threatening severity]. The most common co-reported AEs with photophobia were headache, pyrexia, fatigue, nausea, chills, myalgia, dizziness, arthralgia, pain in extremity, malaise, vomiting, migraine. Also, the onset latency of the majority of AEs of interest were reported in ≤ 7 days (92% (n=1371), out of which 88% (n=1313) were reported in ≤ 3 days. The most common co-reported ocular AEs with a frequency of >1% of all AEs were eye pain (10.2% of all AEs), vision blurred (7.0% of all AEs), visual impairment (2.6% of all AEs), ocular discomfort (1.2% of all AEs) and dry eye (1.1% of all AEs). All the AEs concerning any thromboembolic

phenomenon were less than 1% of all AEs (thrombocytopenia, cerebral venous sinus thrombosis, cerebrovascular accident, thrombosis, portal vein thrombosis).

The most commonly co-reported AEs with the PT of 'Photophobia' is shown in Table 66.

Table 66 Distribution of most frequently co-reported adverse events in cases reporting photophobia with COVID-19 VACCINE ASTRAZENECA, cumulatively through 28 December 2021

Adverse events	Number	Percentage
Photophobia	2069	-
Headache	1576	76.2
Pyrexia	1026	49.6
Fatigue	811	39.2
Nausea	730	35.3
Chills	705	34.1
Myalgia	600	29.0
Dizziness	511	24.7
Arthralgia	450	21.7
Pain in extremity	263	12.7
Malaise	238	11.5
Vomiting	236	11.4
Migraine	221	10.7

Out of 2069 events, outcome for the event of Photophobia was reported as fatal in four cases (PPD) as discussed below:

- PPD : A PPD year old PPD experienced AEs of stroke, photophobia and vomiting after 8 days following vaccination. Cerebral haemorrhage, cerebral infarction, diverticulitis, portal vein thrombosis, thrombocytopenia, cerebral venous sinus thrombosis (CVST) were identified upon medical examination. It was reported that the patient died from the event of thrombocytopenia, thrombus, stroke, thrombus, PPD , consciousness decreased, headache, photophobia, intracerebral haemorrhage, pyelophlebitis, diverticulitis, confusion, portal vein thrombosis, consciousness abnormal and vomiting, 19 days post vaccination. There was insufficient information on extent of CVST, exact death certificate and autopsy details.

  AstraZeneca Comment: As photophobia may be seen in cerebral thrombosis and haemorrhages, it is considered as an early manifestation of cerebrovascular accident, rather than a contributory factor for fatal outcome. Medical history of gastric ulcer, hiatus

hernia, PPD , prediabetes and concomitant use of PPD (unknown indication) and PPD are considered confounders for rapid worsening of neurological status, intraabdominal thrombosis and inflammation.

- PPD : A PPD year old PPD experienced AEs of headache, photophobia and vomiting on the day of vaccination, which worsened further over next 2 weeks leading to hospitalization. Portal vein thrombosis, jugular vein thrombosis, cerebral vein thrombosis (CVT), hepatic vein thrombosis, intestinal ischaemia, hypoperfusion and thrombocytopenia were found upon further medical examination. It was reported that the patient died from the event of portal vein thrombosis, thrombocytopenia and photophobia, 16 days post vaccination. There was insufficient information on extent of CVT, ocular examination, death certificate and autopsy details.

  AstraZeneca Comment: As photophobia may be seen in cerebral venous thrombosis, it is considered as an manifestation of cerebrovascular accident, rather than a contributory event for fatal outcome. Based on the information provided, small bowel ischemia in the backdrop of medical history of hypertension and depression is considered as the primary cause of death.

- PPD : A PPD year old PPD experienced AEs of headache, nausea, vomiting, dizziness and photophobia on the day of vaccination. There was no information on further clinical course of photophobia. Portal vein thrombosis, visceral venous thrombosis, mesenteric vein thrombosis, intestinal ischaemia, and thrombocytopenia were found upon medical examination. It was reported that the patient died from the event of complications of high risk surgery, nausea, vomiting, dizziness, photophobia, small bowel infarction, superior mesenteric thrombosis, thrombosis and thrombocytopenia, 16 days post vaccination. There was insufficient information on clinical course of photophobia, ocular examination and death certificate.

  AstraZeneca Comment: Based on the information provided, small bowel ischemia in the backdrop of complication of high risk surgery is considered as the primary cause of death. Photophobia can be considered as a manifestation of headache however, as there was no information on further exact clinical course of photophobia, a comprehensive causal assessment of fatal outcome of photophobia was not possible.

  PPD : A PPD year old PPD experienced AEs photophobia on a unknown date after vaccination. The co-reported AEs were concerning migraine, systemic thromboembolism (intra-abdominal and pulmonary), thrombocytopenia, contusion (unknown location), musculoskeletal stiffness, cardiac arrest, and gastroenteritis viral etc which could explain the co-existence of photophobia as a co-manifestation. Medical history of migraine, possible subarachnoid haemorrhage and family history of PPD are considered as confounders in the backdrop of acute stressful state.

AstraZeneca comment: Although photophobia is reported with a fatal outcome, the co-reported AEs as discussed above can better explain the worsened clinical condition and fatality. Photophobia can be considered as co-manifestation of migraine, which was co-reported in this case. There was insufficient information on exact clinical course of photophobia and ocular examination.

On review of the four fatal AEs pertaining to photophobia, all were co-reported with other cerebrovascular events in adult PPD vaccinees and in neither of the cases photophobia as primary cause of death. The case information in cases PPD and PPD had many similarities suggesting affection of same patient, however this could not be comprehensively confirmed as the case was from a regulatory source. In the absence of any other ocular symptom, the AEs of photophobia can be considered as manifestation of co-reported cerebrovascular coagulation events or migraine itself rather than a causality for the fatal outcome. The co-reported thrombo-embolic events along with surgery be considered as primary causes of death in the four cases. Additionally, there was insufficient information on ocular examinations for a comprehensive medical assessment.

A total of 28 AEs pertaining to photophobia in 28 cases were reported as life-threatening. However, none of the cases provided the rationale for considering photophobia as life-threatening AE. In 19 out of 28 AEs, a serious concurrent condition was identified which could explain the life-threatening status of the patient (concurrent systemic thrombo-embolic events such as cerebrovascular accident, CVST, intra-abdominal thrombosis in 13 cases; encephalitis or CNS inflammatory conditions such as GBS in three cases; brain abscess, hypotension and hepatic encephalopathy with pre-existing autoimmune hepatitis reported singularly). Photophobia can be considered as co-manifestation of cerebrovascular pathologies rather than an independent determinant of life-threatening status. In the remaining 9 out of 28 cases, there was insufficient information on exact clinical course of events, medical history, concomitant medication, treatment received for a comprehensive causal assessment.

Observed vs. Expected Analysis

In order to perform observed vs. expected analysis reliable and representative background incidence rates are required. When these reliable incidence rates are not available the Vaccine Europe Observed to Expected Analysis Workshop (with representation from several pharmaceutical companies) has determined that performing observed vs. expected analyses is not possible. No reliable background incidence rate was identified for photophobia. Therefore, observed vs. expected analysis on this topic could not be performed.

Literature

AstraZeneca completed a cumulative literature search of the literature in Embase, InsightMeme, and PubMed published through 28 December 2021.

The search yielded 12 relevant articles which were all case reports and are reviewed in detail in Table 67 below.

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
Mehta et al 2021 Case report PPD Vaxzevria vaccine	6 days	PPD		Meningitic headache vomiting petechial rash, gum bleeding, PPD , focal motor seizures	Neuroimaging- superior sagittal sinus thrombosis with extension into the cortical veins, and haemorrhage in lobar and subarachnoid locations.	Photophobia be considered a manifestation of CVST. History of migraines is a strong confounder. PPD with side effect photosensitization; PPD for blurred vision.
Soleimani et al 2021, Case report ChAdOx1 nCoV-19 vaccine PPD	12 days			drowsiness, agitation and right sided weakness, holocephalic headache, vomiting, CVST	CT venogram confirmed an extensive CVST in the superior sagittal sinus extending to both transverse venous sinuses,	The Headache with Photophobia it is most likely occurring in the context of extensive cerebral venous sinus thrombosis (CVST). Also literature presents cases of Photophobia after PPD
Soleimani et al 2021, Case report PPD ChAdOx1 nCoV-19 vaccine	10 days			right calf pain, cold sensation of the limb, left temporal headache., photophobia, phonophobia, nausea, petechial rash across PPD legs and abdomen. left transverse and	CT venogram - left transverse and sigmoid sinus thrombosis with involvement of the sagittal sinus and thrombosed left jugular vein	It is possible that Photophobia occurred in the context of - left transverse and sigmoid sinus thrombosis with involvement of the sagittal sinus and thrombosed left jugular vein.

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
				sigmoid sinus thrombosis		
Casucci and Acanfora 2021 Case report PPD ChAdOx1 nCov-19	within hours	PPD		throbbing headache, nausea, chills, fever (39 °C), muscle and joint pain, and inability to walk mainly due to severe asthenia, disseminated intravascular coagulation		The patient had a history of headaches. Also, the photophobia could have occurred immediately after vaccination together with headache and other flu-like symptoms reactogenicity.
Clark et al 2021 Case report PPD Ad26. COV2. S	12 days		PPD	initially reported - headache, sinus pressure, myalgias, and sore throat with tonsillar exudate. PPD continued to have worsening headaches, especially with movement, associated photophobia, and intermittent dizziness .	thrombocytopenia, increased D-dimer levels, CT showed CVST involving the left transverse and sigmoid sinuses, extending into the left internal jugular vein, with acute subsegmental pulmonary emboli.	Photophobia could have occurred in the context of thrombocytopenia, and CVST. Insufficient information on indication for concomitant medications, and any eye examination. As reported - it is unclear whether the inflammatory response seen in our patient was secondary to a recent asymptomatic COVID infection, PPD vaccination or both.

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
See et al 2021 Case report-1 Adult PPD Ad26.COV2.S	15 days	Unknown	Unknown	Headache, neck pain, nausea, vomiting,	CVST, Right internal jugular vein thrombosis	Possible photophobia occurred in the context of CVST with Thrombocytopenia
See et al 2021 Case reports-2 Adult PPD Ad26.COV2.S	7 days	Unknown	Unknown	Headache, nausea, vomiting, loss of consciousness, seizure, CVST, intracerebral hemorrhage	CVST, intracerebral hemorrhage	Possible photophobia occurred in the context of CVST with Thrombocytopenia
See et al 2021 Case reports-3 Adult PPD Ad26.COV2.S	6 days	Unknown	Unknown	Headache petechial rash, neck pain, body aches, dizziness, CVST, Right pulmonary embolism, left internal jugular vein thrombosis	CVST, Right pulmonary embolism, left internal jugular vein thrombosis	Possible photophobia occurred in the context of CVST with Thrombocytopenia
Abousy et al 2021, Case report PPD Pfizer COVID-19 vaccination	8 days	Unknown	Unknown	Bilateral Corneal transplant rejection	uncorrected visual acuity was 20/70 and 20/40. Central corneal thickness was 809 and 825 µm Slit-lamp biomicroscopy revealed quiet conjunctiva and sclera	History of burning and blurred vision after 6years of transplantation No etiological work up. Reported incidence of graft failure over a longer follow-up of 5-10 years [van Rooji et al 2018; Hjortdal et al 2013] following common surgical techniques for corneal transplantation as uncommon

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
					but was significant for thickened corneas with Descemet folds in both eyes	frequency (5-11%). In view of unilateral presentation, no symptom after first vaccination dose and presence of corneal pathology, the causal role of Pfizer COVID-19 vaccination for photophobia is considered unlikely.
Bangash et al 2021 Case report PPD J&J COVID-19 vaccine	unknown	PPD	Unknown	PPD Seizures, PPD	MRI brain showed diffuse nonspecific white matter signal abnormalities. Ferritin of 937 mcg/L, and CRP of 47.3 mg/L and an elevated NT-proBNP PPD on bone marrow examination	Insufficient discussion on onset, duration, etiological workup and treatment received for photophobia. It is possible that Photophobia occurred in the context of seizures and encephalopathy.
Dias et al 2021, Case report PPD BNT162b2, Comirnaty	6 days		none	cerebral venous sinus thrombosis, headache, nausea, vomiting	Brain MRI with venography revealed thrombosis of superior sagittal, right lateral, transverse, sigmoid sinuses and jugular vein	Concurrent papilledema, left visual extinction, right gaze deviation point to a cortical mechanism of photophobia secondary to cerebral venous and venous sinus thrombosis and is a known manifestation of cerebrovascular accidents. Underlying mechanisms for

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
					and left sigmoid sinus, together with right frontal subarachnoid hemorrhage and a cortical venous infarct	adenomyosis could also possible explain the thrombotic milieu.
Li S et al 2021 Case report PPD Sinovac	2 days	PPD		herpes simplex viral (HSV) dendritic lesion	slit-lamp examination showed a typical herpes simplex viral (HSV) dendritic lesion in the corneal graft center	Etiological workup indicated a typical herpes simplex viral (HSV) dendritic lesion in the corneal graft center which can explain the photophobia and worsened vision. TTP for Herpes in 2 days is considered unlikely. There was no information of any contaminated batch. Also, in the backdrop of reported incidence of graft failure over a longer follow-up of 5-10 years [van Rooji et al 2018; Hjortdal et al 2013] following common surgical techniques for corneal transplantation as uncommon frequency (5-11%), a history of herpes simplex keratitis, and unlikely temporal plausibility, a causal role of vaccine for can be considered unlikely.

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
Phylactou et al 2021, Case report-1 PPD Pfizer-BioNTech	7	PPD		Blurred vision, redness	slit lamp examination, anterior segment findings included moderate conjunctival injection, diffuse corneal oedema, fine keratic precipitates restricted to the donor endothelium inferiorly, inflammation.	PPD or Immune reconstitution inflammatory syndrome following recently increased gap in between steroid doses could be possible confounder.
Phylactou et al 2021 Case report-2 PPD Pfizer-BioNTech	21 days to 2nd dose			sudden onset of bilateral blurred vision, pain, photophobia and redness	slit lamp examination included bilateral circumcorneal injection, keratic precipitates, Anterior Chamber inflammation and normal intraocular pressure	Bilateral affection suggests possibility of systemic insult. No similar complaints after 1st dose but only after 2nd dose point to a possible incidental occurrence. Insufficient information on other medical history. Reported incidence of graft failure over a longer follow-up of 5-10 years [van Rooji et al 2018; Hjortdal et al 2013] following common surgical techniques for corneal transplantation is uncommon frequency (5-11%) and possibly may explain the AE.

Table 67 Review of literature corresponding to AE of photophobia and COVID-19 vaccine

Authors Type of study Patient demographics Vaccine type	TTO	Medical history	Concomitant medications	Other co-reported events	Relevant investigations	AstraZeneca comment
						Possible photophobia occurred in the context of corneal inflammation.

CT Computed Tomography, CVST Cerebral venous sinus thrombosis, F Female, HLH Hemophagocytic lymphohistiocytosis, M Male, MRI Magnetic resonance imaging, TTO Time to onset, Y Years.

On review of the 14 case reports in 12 articles, four were reported for mRNA vaccines, nine were reported for viral vector vaccines and one was reported for inactivated virus vaccine. Twelve (12) case reports were reported following 1st dose of the vaccination, and 2 case reports were following 2nd dose of the vaccination. In all the 14 case reports, photophobia was co-reported with events of cortical pathology [cerebrovascular thromboembolism (including venous sinuses), n=10] or ocular pathology (anterior chamber inflammation with corneal rejection, n=4) and none of the case reports reported occurrence of photophobia in isolation. The cortical and ocular pathologies as described above have been known to manifest as photophobia. The median latency of approximately 7 days also supports the occurrence of photophobia as a co-manifestation. Possible confounders were also identified in 11 case reports such as previous corneal transplant, recent down titration of concomitant topical steroids prior to vaccination, HIV infection, medical history of migraine, headache, lithium use and so on. Also, in view of comorbid conditions which could explain the AE of photophobia, there is limited scope for extrapolation of case report findings to all COVID-19 vaccines.

Summary

A slight majority of the AEs of photophobia were reported as serious (1055 AEs, 51%). Out of 1055 serious AEs, 707 (67%) had seriousness criteria of medically important event, however, only 6.5% (45 AEs) were reported as being medically confirmed. The majority of the retrieved serious AEs pertaining to photophobia (86%. 905 out of 1055) originated from the UK, most of which were not medically confirmed (94%). This finding is in line with WHO's remark about the confounder represented by the cluster of cases due to mass vaccination of the UK population with AZ vaccine. Moreover, the UK patients are permitted to report adverse events and judge by themselves the AE seriousness via the Yellow Card System, and this could be the reason for the observed high proportion of serious events/cases for photophobia. A review of fatal and life-threatening AEs of photophobia did not raise any significant safety concern.

The majority of AEs of photophobia were experienced in the reactogenicity period of the vaccine thus making the TTO reasonable (WHO-UMC as possible) but were co-reported with known reactogenicity events or migraine itself. In fact only 1% of photophobia events was reported as singular AE with majority non-serious with favourable outcome. The majority of AE outcome in total were favourable (recovered or recovering) (56%). Additionally, the mean and median duration of the photophobia AEs of 3.8 days and 2 days respectively which majorly suggests a short duration of AE in the backdrop of onset predominantly in the reactogenic period of the vaccine. There was no significant trend in either the frequency or the type of co-reported ocular AEs or AEs concerning thromboembolic phenomenon.

The medical history was reported in only 968 of the 2069 (47%). The most common medical histories in descending order of frequency were COVID-19 or suspected COVID-19, asthma, migraine or headache, immunodeficiency, hypertension, fibromyalgia, drug hypersensitivity, seasonal allergy and hypersensitivity. This suggests a possible pre-existing hormonal (possibly explaining the more female gender distribution), migraine susceptibility or allergic milieu. A common medical history of migraine / headache (suggesting individual predisposition) in the backdrop of common co-reported AE of migraine / headache may be considered as plausible explanation for photophobia coinciding with reactogenic period of the vaccine and short-lived duration.

In summary, on review of AstraZeneca safety database, based on insufficient case details (on medical history, concomitant medications, ocular examination) or based on predominant onset within the reactogenic period, short duration, predisposition by pre-existing migraine or concurrent migraine, no significant trend in ocular or thromboembolic vascular symptoms, a direct causal relationship of photophobia to vaccine administration cannot be comprehensively confirmed.

On review of all available literature cumulatively till the DLP of this PBRER which comprised case reports, either alternate explanations in the form of co-morbidities were identified for the manifestation of photophobia or there was insufficient information (such as relevant ocular examinations, clinical course of the AE of photophobia).

Conclusion:

In summary, there is no evidence to conclude that the reported cases of Photophobia, can be directly related to COVID-19 VACCINE ASTRAZENECA. The company does not consider that an update to the CDS or RMP for COVID-19 VACCINE ASTRAZENECA is warranted. Events of photophobia will continue to be monitored as part of AstraZeneca's routine surveillance activities.

15.2.17 Retinal arterial/venous thrombosis, embolism, or occlusion

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021:

"The MAH is requested to provide a cumulative review of retinal arterial/venous thrombosis, embolism, or occlusion, jointly with an O/E analysis and a discussion of TTO, risk factors, outcome of the cases and causality assessment."

AstraZeneca's response to this request is provided below.

Review of Cases:

A cumulative search of the AstraZeneca global safety database through 28 December 2021 was conducted to identify cases of Retinal arterial/venous thrombosis, embolism, or occlusion with COVID-19 ASTRAZENECA VACCINE. The PTs used to define Retinal arterial/venous thrombosis, embolism, or occlusion included: Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Retinal vascular thrombosis and Retinal vascular occlusion.

The search identified a total of 506 cases with 536 events which included 521 PTs in vaccinees who received COVID-19 VACCINE ASTRAZENECA. The Adverse event PT counts were: Retinal vein occlusion (264), Retinal artery occlusion (83), Retinal vein thrombosis (80), Retinal vascular thrombosis (45), Retinal artery thrombosis (24), Retinal artery embolism (13) and Retinal vascular occlusion (12).

Of the 506 cases, 266 (52.6%) cases occurred in females, 231 (45.7%) occurred in males and the gender was unknown in 9 (1.8%) cases. The reports were from post-marketing sources with 497 Spontaneous cases (98.2%), 5 (1%) cases from Non-interventional studies and 4 (0.8%) Literature cases. Of the 506 cases, 262 (52%) were medically confirmed (261 reported as serious and 1 reported as non- serious), and 500 (98.8%) were reported as serious. Reported seriousness criteria included: fatal (1), life threatening (11), hospitalization (65), disability (140) and medically significant (376). The fatal case (PPD) has been described below.

Out of the 506 reports, 139 were from the United Kingdom, 78 were from France, 46 were from Italy, 45 were from Germany, 44 were from Australia, 27 were from Netherlands, 18 were from Spain, 17 were from Brazil, 16 were from Sweden, 15 were from Belgium, 9 were from Portugal, 7 were from Finland, 6 were from Greece, 5 were from Austria, 4 were from Hungary and India each, 3 were from Ireland and Norway each, 2 each were from Cyprus, Estonia, Mexico, Philippine and Poland, 1 each were from [redacted]

The age range of these vaccinees was between 20 and 92 years. Median age was 64 years. Two hundred forty-four (48.2%) vaccinees were between the ages of 18 to 65 years, 222 (43.9%) were >65 years and in 34 (6.7%) cases the age was unknown. 32 cases occurred after the first dose, 68 cases occurred after the second dose and in 406 cases dose information was not provided.

The 506 cases had 536 retinal vascular occlusive events and the outcome of the events were not recovered for 280 events cases, recovering for 75 events, recovered for 34 events, recovered with sequelae for 33 events. The outcome was unknown in 114 events.

The time to onset (TTO) of the events ranged between 0 and 201 days, median TTO was 14 days. 288 events occurred within 0-28 days, 45 events within 29 -42 days and 58 events

occurred after 42 days. TTO was unknown for 145 events. 69 events occurred after the second dose; of the 69 events 26 events occurred between 0 and 28 days, 6 events occurred between 29 and 42 days and 12 events occurred after 42 days. TTO for 15 events was unknown.

In 3 cases, there were retinal events after the first dose and thrombotic events in other sites after the second dose. In case PPD, the patient experienced retinal vein occlusion after the first dose and splenoportal axis thrombosis after the second dose. In case PPD, the patient developed blood clot in the right eye 3 weeks after the first dose and swelling in the right leg 10 days after 2nd dose probably due to thrombosis. In case PPD, patient experienced blood clots in the right eye 10 days after the first dose and swelling of the right leg 10 days after the 2nd dose; it was not reported if the swelling in the right leg was due to a thrombotic cause. Cases PPD might be possible duplicates.

Most commonly reported co-reported events in the 506 cases included: Headache (41), Vision blurred (31), Visual impairment (29), Blindness (24), Macular oedema (19), Blindness unilateral (17), Visual acuity reduced (16), Pyrexia (14), Chills (12), Nausea (12), Thrombosis (11), Hypertension (10), Retinal haemorrhage (10), Malaise (8), Blood pressure increased (7), Fatigue (7), Myalgia (7), Pulmonary embolism (7), Visual field defect (7), Cerebrovascular accident (6), Dizziness (6), Thrombocytopenia (6), Cystoid macular oedema (5), Eye pain (5) and Migraine (5).

These 506 cases were assessed for causality according to the WHO-UMC classification. Based on this classification 324 cases were assessed as possible, 125 cases were unassessable as the TTO was not provided to make an assessment and 57 cases were unlikely as they occurred outside the 42 day risk window. The rational for selection of the RW is provided in the ‘Observed versus Expected Analysis’ section below.

The 324 cases were assessed as possible as they had occurred within the 42 days risk window for TTO. In 141 of 324 cases the information was limited in regards to the vaccinees’ medical history, comorbidities, concomitant medications, etc. The assessment in the remaining 183 cases was based on a reasonable TTO (within 42 days) although the event could also have alternative explanations (vaccinees’ underlying diseases, confounding events, medical or ocular history and concomitant medications). The most common confounding events and history present in these 183 cases included: hypertension, diabetes, dyslipidemia, atrial fibrillation, migraine, myocardial infarction, carotid artery thrombosis, hypercholesterolemia, smoking. Most common concomitant medications indicating alternate etiologies or medical history included heparin, amlodipine, atorvastatin, losartan, simvastatin, bisoprolol, metformin, ramipril. Past Ocular history present in these cases were glaucoma, central retinal vein occlusion, central vein thrombosis, retinal vein thrombosis, cataract and uveitis.

Important modifiable risk factors associated with Retinal arterial occlusion/ Retinal emboli have been discussed by Mac Grory et al 2021 and also provided in Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern by the American Association of Ophthamology. These included: obesity, hypertension, tobacco use, hypercholesterolemia, diabetes, cardiac arrhythmia, cardiac valvular disease, heart failure, coagulopathy and cardiac disease. Systemic risk factors for Retinal vein occlusion were listed by Rehak and Wiedmann 2010 and Wong and Scott 2010, these included: hypertension, hyperlipidemia, diabetes mellitus, atherosclerotic vascular disease: coronary artery disease, high body mass index, smoking, renal disease, vasculitis (systemic lupus erythematosus, sarcoid, syphilis), neoplasia (polycythemia rubra vera, multiple myeloma, leukemia), drugs (oral contraceptives, diuretics) and Ocular risk factors such as glaucoma or elevated intraocular pressure, which may compromise retinal venous outflow).

There was one case (PPD) with fatal outcome as discussed below:

PPD **:** A spontaneous report from PPD was received of a PPD with no reported age. Past and current medical history included PPD . No concomitant products were reported. The vaccinee experienced clot blood (PT: Thrombosis) on the following month after receiving the vaccine. On an unknown date, the patient experienced retinal venous thrombosis (PT: Retinal vein thrombosis), platelet count <150 a 109/l (preferred term: Thrombocytopenia), venous haemorrhage (preferred term: Venous haemorrhage), PPD and lower limb ischaemia (preferred term: Peripheral ischaemia). It was reported that the patient experienced retinal venous thrombosis - possibly due to the clots. Computerised tomography (CT) confirmed various clots around the body. Platelets were less than 10 and had not tested positive for COVID-19 since having the vaccine. The outcome of the event(s) of retinal venous thrombosis, platelet count <150 a 109/l, venous haemorrhage, PPD and lower limb ischaemia was unknown. The vaccinee died from the event of clot blood, the exact date was not reported. It was not known whether an autopsy was performed.

AstraZeneca Comment: Confounded by the risk factor of peripheral vascular disease and the co-reported event of Thrombosis and Thrombocytopenia. No reported age, concomitant medication, time to onset, ophthalmic history/assessments/investigation.

AstraZeneca assessed this case as Possible according to WHO-UMC criteria. In addition, AstraZeneca classified this case as Possible using the MHRA case classification for TTS.

Cases with thrombotic events

Eleven out of the 506 cases had included events of Thrombosis and thrombocytopenia. These case reports were reviewed in accordance with the MHRA case definition for thrombosis in combination with thrombocytopenia. Based on this classification, 7 were assessed as ‘criteria

not met', 3 as 'possible' and 1 as confirmed. Of the 11 cases with events of Thrombosis and thrombocytopenia, 1 case had fatal outcome and is discussed below. Common thrombotic PTs in these cases included: Thrombocytopenia (6), Immune thrombocytopenia (3), Thrombosis with Thrombocytopenia syndrome (3), Thrombosis (2), Heparin-induced thrombocytopenia (2). These cases had thrombosis events in other sites in addition to the retinal vessels. The adverse event PTs in these cases involving other sites included: Cerebral venous sinus thrombosis, Cerebral venous thrombosis, Carotid artery occlusion, Jugular vein thrombosis, Pulmonary embolism, Transverse sinus thrombosis, Venous thrombosis, Ischaemic stroke, Embolism, Hemiplegia, Infarction, Intestinal infarction, Mesenteric vascular occlusion, Splenic infarction, Portosplenomesenteric venous thrombosis and Cerebrovascular accident. Of the remaining 495 cases, 456 cases had retinal thrombotic PTs as the only thrombotic PT reported, and 39 cases had thrombosis at other sites reported. The other Thrombotic PTs reported in these cases included Arterial occlusive disease, Carotid artery thrombosis, Cerebral artery thrombosis, Cerebrovascular accident, Deep vein thrombosis, Embolism, Infarction, Ischaemic stroke, Myocardia linfarction, Ophthalmic vein thrombosis, Pulmonary embolism, Transient ischaemic attack, Venous occlusion and Venous thrombosis.

The case (PPD) with fatal outcome is discussed below:

PPD **:** A spontaneous report from PPD was received of a PPD with no reported age. Past and current medical history included PPD No concomitant products were reported. The vaccinee experienced clot blood (PT: Thrombosis) on the following month after receiving the vaccine. On an unknown date, the patient experienced retinal venous thrombosis (PT: Retinal vein thrombosis), platelet count <150 a 109/l (preferred term: Thrombocytopenia), venous haemorrhage (preferred term: Venous haemorrhage), PPD and lower limb ischaemia (preferred term: Peripheral ischaemia). It was reported that the patient experienced retinal venous thrombosis - possibly due to the clots. Computerised tomography (CT) confirmed various clots around the body. Platelets were less than 10 and had not tested positive for COVID-19 since having the vaccine. The outcome of the event(s) of retinal venous thrombosis, platelet count <150 a 109/l, venous haemorrhage, PPD and lower limb ischaemia was unknown. The vaccinee died from the event of clot blood, the exact date was not reported. It was not known whether an autopsy was performed.

AstraZeneca Comment: Confounded by the risk factor of peripheral vascular disease and the co-reported event of Thrombosis and Thrombocytopenia. No reported age, concomitant medication, time to onset, ophthalmic history/assessments/investigation

AstraZeneca (AZ) WHO-UMC causality: Possible

MHRA Case Classification for TTS: Possible

Cases reported from the literature

Four cases were identified in the global safety database as being reported from the literature. These cases are summarized below.

- PPD: Kim et al 2021 presented a case report of a PPD year old PPD with blurred vision in the PPD eye. No abnormal finding in the left eye was observed until two months ago, and PPD had no documented past medical history including hypertension and diabetes. PPD received COVID-19 vaccine (ChAdOx1 nCoV-19 vaccine, AZD1222) and experienced blurred vision 1 day afterwards. Best corrected visual acuity (BCVA) was 20/25 in the left eye. Multiple retinal hemorrhages were found on entire retina in the fundus examination. Moreover, FFA presented multiple thrombosis in the peripheral retinal veins (preferred term: Retinal vein thrombosis). However, definite non-perfusion, capillary dropout, microaneurysm and neovascularization were not observed, and arm-to-retinal time was not delayed. There was no macular edema in the optical coherence tomography (OCT). After 2 months, BCVA of the patient was decreased to 20/200 and macular edema was observed in the OCT scan. The author concluded that COVID-19 vaccination can induce multiple retinal hemorrhage with retinal vein thrombosis, which may be considered as a kind of thrombolytic thrombosis syndrome in the retinal vasculature.

AstraZeneca Comment: WHO-UMC Causality assessed as Possible due to temporal association; however, the patient had co-reported event of Thrombosis with thrombocytopenia syndrome that could be an alternate etiology for the event. No reported concomitant medication, ophthalmic history, laboratory results. This case did not meet criteria for Thrombosis with Thrombocytopenia syndrome using the MHRA classification.

There were two cases from the literature article (Sonawane et al 2021): PPD and PPD.

- PPD: This case involves a PPD year old PPD who presented with PPD eye diminution of vision 4 days after receiving the second dose of Covishield vaccine. The best-corrected visual acuity was OD 6/60 and OS 6/6. The fundus examination revealed disk edema, dilated and tortuous veins, diffuse retinal hemorrhages with macular edema, suggestive of central retinal vein occlusion. The PPD eye fundus showed mild non-proliferative diabetic retinopathy changes. The optical coherence tomography showed cystoid macular edema with a central foveal thickness of 571 um in the PPD eye. The lab reports revealed uncontrolled diabetes with HbA1C of 13.2 with deranged renal profile (blood urea: 80 mg/dL, creatinine: 1.9 mg/dL), PPD was given intravitreal injection anti-vascular endothelial growth factor (VEGF) for cystoid macular edema. The authors stated that there were reports on vascular thromboembolic catastrophes post-vaccination, especially with ChAdOx1 and proposed possible hypothesis of underlying pathophysiology.

AstraZeneca Comment: WHO-UMC Causality assessed as Possible due to temporal association; however, the patient's medical history of diabetes presents a potential alternative explanation. No reported concomitant medication, ophthalmic history, laboratory results.

- PPD: This case involves a PPD year old PPD with unremarkable history who presented with PPD eye sudden-onset dimunition of vision 3 days after receiving the second dose of Covishield vaccine. PPD best-corrected visual acuity was OD 5/60 and OS 6/12. The anterior segment examination showed an immature senile cataract in both eyes and dense central posterior subcapsular in right eye (OD). The intraocular pressure was within normal limits in both eyes. The fundus examination of the PPD eye showed hyperemic and edematous disk, tortuous veins, and intraretinal hemorrhages in all quadrants suggestive of impending central retinal vein occlusion. Blood investigations revealed raised erythrocyte sedimentation rate (ESR): 49, CRP 14.6 (n: <5), rheumatoid factor (RF) 11 (n: <8) and d-dimer 6077.4 ng/mL, (n: <500). Patients was followed up till resolution of retinal hemorrhages. The authors stated that there were reports on vascular thromboembolic catastrophes post-vaccination, especially with ChAdOx1 and proposed possible hypothesis of underlying pathophysiology.

AstraZeneca Comment: WHO-UMC Causality assessed as Possible due to temporal association; however, there were no reported concomitant medication, ophthalmic history, laboratory results that could be alternate aetiology for the event.

- PPD: This case involves a PPD year old PPD patient who presented to the ophthalmology emergency clinic complaining of sudden, painless vision loss in PPD eye of 24 hours duration. The patient had received Vaxveria seven days prior to the presentation. The clinical and fundus examination of the right eye revealed set the diagnosis of Branch retinal vein occlusion. The outcome of the event was unknown. In the present case, the authors discussed that the BRVO occurred during the COVID-19 period. The close temporal relationship between the BRVO incidence and the vaccination with Vaxzevria is reinforced by the lack of another subjective cause to justify the episode.

AstraZeneca Comment: WHO-UMC Causality assessed as Possible due to temporal association; however, there were no reported concomitant medication, ophthalmic history, laboratory results that could be alternate etiology for the event.

Observed versus Expected Analysis

The Observed versus expected analysis for all cases of Retinal occlusion is presented with a risk window of 42 days and 28 days in Table 68. The risk window of 28 days has been agreed with Vaccine Europe for thrombosis, and the RW of 42 days is used conservatively as most of the events are reported within 42 days.

The number of observed cases were provided for both risk windows with and without cases with unknown time to onset as a conservative approach.

For incidence rates, the publication, Pick et al 2020, was used, as the incidence rates reference as it contained age specific rates presented. The limitation is that the publication is only on arterial occlusion, and does not cover venous events, thus this is a conservative approach.

Table 68 Observed Versus Expected analysis for retinal artery occlusion cases overall (Global) including unknown TTO

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
Overall	285	4560.73	42	13.6	291626957	0.06 (0.06 - 0.07)	Observed significantly < expected
Overall (Including unknown TTO)	421	4560.73	42	13.6	291626957	0.09 (0.08 - 0.1)	Observed significantly < expected
Overall	240	3040.49	28	13.6	291626957	0.08 (0.07 - 0.09)	Observed significantly < expected
Overall (Including unknown TTO)	376	3040.49	28	13.6	291626957	0.12 (0.11 - 0.14)	Observed significantly < expected

a Pick et al 2020. Incidence of retinal artery occlusion in Germany. Acta Ophthalmologica 2020
CI Confidence Interval; E Expected; O Observed; TTO Time to onset

Additionally, the observed versus expected analysis is presented with stratification by age for the EU, UK regions based on the available exposure data, this is presented in Table 69 and Table 70.

Table 69 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
20 to 24	1	1.09	42	1	947500	0.92 (0.02 - 5.11)	Observed < expected
25 to 29	1	2.7	42	2	1173684	0.37 (0.01 - 2.06)	Observed < expected
30 to 34	0	3.78	42	2	1644841	0 (0 - 0.98)	Observed significantly < expected

Table 69 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
35 to 39	2	4.68	42	2	2034497	0.43 (0.05 - 1.54)	Observed < expected
40 to 44	4	22.27	42	4	4842664	0.18 (0.05 - 0.46)	Observed significantly < expected
45 to 49	0	24.62	42	4	5352648	0 (0 - 0.15)	Observed significantly < expected
50 to 54	6	45.78	42	6	6634875	0.13 (0.05 - 0.29)	Observed significantly < expected
55 to 59	7	45.82	42	6	6641536	0.15 (0.06 - 0.31)	Observed significantly < expected
60 to 64	5	90.4	42	14	5615191	0.06 (0.02 - 0.13)	Observed significantly < expected
65 to 69	6	145.26	42	30	4210819	0.04 (0.02 - 0.09)	Observed significantly < expected
70 to 74	12	189.96	42	41	4029078	0.06 (0.03 - 0.11)	Observed significantly < expected
75 to 79	5	123.62	42	39	2756426	0.04 (0.01 - 0.09)	Observed significantly < expected
80+	1	143.03	42	45	2764092	0.01 (0 - 0.04)	Observed significantly < expected
20 to 24	1	0.73	28	1	947500	1.37 (0.03 - 7.63)	Observed > expected
25 to 29	1	1.8	28	2	1173684	0.56 (0.01 - 3.1)	Observed < expected
30 to 34	0	2.52	28	2	1644841	0 (0 - 1.46)	Observed < expected

Table 69 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
35 to 39	2	3.12	28	2	2034497	0.64 (0.08 - 2.32)	Observed < expected
40 to 44	3	14.85	28	4	4842664	0.2 (0.04 - 0.59)	Observed significantly < expected
45 to 49	0	16.41	28	4	5352648	0 (0 - 0.22)	Observed significantly < expected
50 to 54	5	30.52	28	6	6634875	0.16 (0.05 - 0.38)	Observed significantly < expected
55 to 59	5	30.55	28	6	6641536	0.16 (0.05 - 0.38)	Observed significantly < expected
60 to 64	4	60.27	28	14	5615191	0.07 (0.02 - 0.17)	Observed significantly < expected
65 to 69	6	96.84	28	30	4210819	0.06 (0.02 - 0.13)	Observed significantly < expected
70 to 74	11	126.64	28	41	4029078	0.09 (0.04 - 0.16)	Observed significantly < expected
75 to 79	3	82.41	28	39	2756426	0.04 (0.01 - 0.11)	Observed significantly < expected
80+	1	95.35	28	45	2764092	0.01 (0 - 0.06)	Observed significantly < expected
20 to 24 (Including Unk TTO)	1	1.09	42	1	947500	0.92 (0.02 - 5.11)	Observed < expected
25 to 29 (Including Unk TTO)	1	2.7	42	2	1173684	0.37 (0.01 - 2.06)	Observed < expected

Table 69 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
30 to 34 (Including Unk TTO)	0	3.78	42	2	1644841	0 (0 - 0.98)	Observed significantly < expected
35 to 39 (Including Unk TTO)	3	4.68	42	2	2034497	0.64 (0.13 - 1.87)	Observed < expected
40 to 44 (Including Unk TTO)	6	22.27	42	4	4842664	0.27 (0.1 - 0.59)	Observed significantly < expected
45 to 49 (Including Unk TTO)	4	24.62	42	4	5352648	0.16 (0.04 - 0.42)	Observed significantly < expected
50 to 54 (Including Unk TTO)	13	45.78	42	6	6634875	0.28 (0.15 - 0.49)	Observed significantly < expected
55 to 59 (Including Unk TTO)	10	45.82	42	6	6641536	0.22 (0.1 - 0.4)	Observed significantly < expected
60 to 64 (Including Unk TTO)	12	90.4	42	14	5615191	0.13 (0.07 - 0.23)	Observed significantly < expected
65 to 69 (Including Unk TTO)	15	145.26	42	30	4210819	0.1 (0.06 - 0.17)	Observed significantly < expected
70 to 74 (Including Unk TTO)	18	189.96	42	41	4029078	0.09 (0.06 - 0.15)	Observed significantly < expected
75 to 79 (Including Unk TTO)	10	123.62	42	39	2756426	0.08 (0.04 - 0.15)	Observed significantly < expected
Over 80 (Including Unk TTO)	2	143.03	42	45	2764092	0.01 (0 - 0.05)	Observed significantly < expected
20 to 24 (Including Unk TTO)	1	0.73	28	1	947500	1.37 (0.03 - 7.63)	Observed > expected

Table 69 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	Background rates [a]	Exposure	O over E ratio (95% CI)	Conclusion
25 to 29 (Including Unk TTO)	1	1.8	28	2	1173684	0.56 (0.01 - 3.1)	Observed < expected
30 to 34 (Including Unk TTO)	0	2.52	28	2	1644841	0 (0 - 1.46)	Observed < expected
35 to 39 (Including Unk TTO)	3	3.12	28	2	2034497	0.96 (0.2 - 2.81)	Observed < expected
40 to 44 (Including Unk TTO)	5	14.85	28	4	4842664	0.34 (0.11 - 0.79)	Observed significantly < expected
45 to 49 (Including Unk TTO)	4	16.41	28	4	5352648	0.24 (0.07 - 0.62)	Observed significantly < expected
50 to 54 (Including Unk TTO)	12	30.52	28	6	6634875	0.39 (0.2 - 0.69)	Observed significantly < expected
55 to 59 (Including Unk TTO)	8	30.55	28	6	6641536	0.26 (0.11 - 0.52)	Observed significantly < expected
60 to 64 (Including Unk TTO)	11	60.27	28	14	5615191	0.18 (0.09 - 0.33)	Observed significantly < expected
65 to 69 (Including Unk TTO)	15	96.84	28	30	4210819	0.15 (0.09 - 0.26)	Observed significantly < expected
70 to 74 (Including Unk TTO)	17	126.64	28	41	4029078	0.13 (0.08 - 0.21)	Observed significantly < expected
75 to 79 (Including Unk TTO)	8	82.41	28	39	2756426	0.1 (0.04 - 0.19)	Observed significantly < expected
Over 80 (Including Unk TTO)	2	95.35	28	45	2764092	0.02 (0 - 0.08)	Observed significantly < expected

a Pick et al 2020. Incidence of retinal artery occlusion in Germany. Acta Ophthalmologica 2020

CI Confidence Interval; E Expected; O Observed; TTO Time to onset; UK United Kingdom; Unk Unknown

Table 70 Observed Versus Expected analysis for retinal artery occlusion cases stratified by age from EEA/UK (including unknown TTO)

Description	Observed Cases	Expected Cases	Risk window	BG rates[a]	Exposure	O over E ratio (95% CI)	Conclusion
18 to 24	3	2.53	42	1	2200746	1.19 (0.24 - 3.47)	Observed > expected
25 to 49	31	82.15	42	2.8	25513352	0.38 (0.26 - 0.54)	Observed significantly < expected
18 to 24 (Including Unk TTO)	3	2.53	42	1	2200746	1.19 (0.24 - 3.47)	Observed > expected
25 to 49 (Including Unk TTO)	38	82.15	42	2.8	25513352	0.46 (0.33 - 0.63)	Observed significantly < expected
18 to 24	3	1.69	28	1	2200746	1.78 (0.37 - 5.19)	Observed > expected
25 to 49	24	54.76	28	2.8	25513352	0.44 (0.28 - 0.65)	Observed significantly < expected
18 to 24 (Including Unk TTO)	3	1.69	28	1	2200746	1.78 (0.37 - 5.19)	Observed > expected
25 to 49 (Including Unk TTO)	31	54.76	28	2.8	25513352	0.57 (0.38 - 0.8)	Observed significantly < expected

a Pick et al 2020. Incidence of retinal artery occlusion in Germany. Acta Ophthalmologica 2020

BG Background; CI Confidence Interval, E Expected; O Observed; TTO Time To Onset, Unk Unknown

The observed versus expected analysis for all cases with a risk window of 42 and 28 days showed that the observed cases were significantly less than expected with and without unknown TTO. The cases were further stratified by age. In the EU/ UK region the observed was greater than expected in the age range 18-24 years though not significantly. In UK only, the observed cases were greater than expected in the ages 20 -24 (with and without cases with unknown TTO) in the 28 day risk window. The observed cases for all other age groups in the EU/ UK region or UK only were either less than expected or were significantly less than expected. A detailed review of cases (n=5) between 18-24 years in the EU/UK and UK only regions is presented in Table 71. For WHO-UMC causality: 1 of the 5 cases was unassessable

due to unknown time between vaccine administration and onset of events, this case also had co-reported events including thrombosis with thrombocytopenia syndrome; 3 cases were assessed as possible due to a reasonable time to onset, however, limited information was available in these cases to make any further assessment; 1 case was assessed as unlikely due to a longer TTO of 75 days and concomitant conditions, medical history in this case suggest alternate aetiologies.

Table 71 Cases in the age group 18-24 years in the EU/UK region

Patient ID/ Serious (Y/N)/ Medically confirmed (Y/N)	Age (years) / Gender (M/F)	Country of origin	Verbatim (AE Preferred Term)	Co-reported events Reported	AE Outcome	Dose#/ TTO (days)	Concomitant meds/ Medical history/ Ocular history	WHO-UMC Causality Assessment/Comment
PPD / Y/ Y	PPD	PPD	PPD (Retinal vein occlusion)	Vision blurred, Chills	Not recovered	1/ 2 days	Not Reported	Based on WHO-UMC classification, the causality assessment is Possible due to temporal association. However, the case contained limited information. No reported relevant medical history, concomitant medication, ophthalmic history/ assessments/investigations
PPD / Y/ Y	PPD	PPD	PPD (Retinal vein occlusion)	Thrombocytopenia, Cerebral venous sinus thrombosis, Headache, Jugular vein thrombosis, Thrombosis with thrombocytopenia syndrome, Pulmonary embolism, Vomiting; Haematoma, PPD	Unknown	1/ unknown	Not Reported	Based on WHO-UMC AstraZeneca has assessed this case as "Unassessable" due to no information regarding time to onset. AstraZeneca has assessed this case as "Confirmed" according to the MHRA classification for TTS. Co-reported events of Thrombocytopenia;Cerebral venous sinus thrombosis, Jugular vein thrombosis, Thrombosis with thrombocytopenia syndrome, Pulmonary embolism, PPD

Table 71 Cases in the age group 18-24 years in the EU/UK region

Patient ID/ Serious (Y/N)/ Medically confirmed (Y/N)	Age (years) / Gender (M/F)	Country of origin	Verbatim (AE Preferred Term)	Co-reported events Reported	AE Outcome	Dose#/ TTO (days)	Concomitant meds/ Medical history/ Ocular history	WHO-UMC Causality Assessment/Comment
				PPD ia, Pyrexia, Suspected COVID-19, Condition aggravated, C-reactive protein increased, Soft tissue necrosis, Transverse sinus thrombosis, Nausea, Migraine				PPD Suspected COVID-19, Transverse sinus thrombosis and Migraine explain the development of the event retinal vein occlusion. No reported relevant medical history, concomitant medication, opthalmic history/assessments/investigations
PPD / Y/ Y	PPD	PPD	PPD (Retinal artery occlusion)		Not recovered	1/ 75 days	PPD	Based on WHO-UMC classification, the causality assessment is "Unlikely" due to the time to onset >42 days. No reported ophthalmic history/assessments/investigations, labs; Time to onset >42 days

Table 71 Cases in the age group 18-24 years in the EU/UK region

Patient ID/ Serious (Y/N)/ Medically confirmed (Y/N)	Age (years) / Gender (M/F)	Country of origin	Verbatim (AE Preferred Term)	Co-reported events Reported	AE Outcome	Dose#/ TTO (days)	Concomitant meds/ Medical history/ Ocular history	WHO-UMC Causality Assessment/Comment
							PPD	
PPD / Y / N	PPD	PPD	PPD (Retinal artery occlusion)		Not recovered	1/ 12 days	Not Reported	Based on WHO-UMC classification, the causality assessment is possible due to temporal association. However, the case contained limited information. No reported relevant medical history, concomitant medication, ophthalmic history/ assessment/investigations
PPD / Y/ N	PPD	PPD	PPD (Retinal artery occlusion)		Not recovered	1/ 2 days	Not Reported	Based on WHO-UMC classification, the causality assessment is possible due to temporal association. However, the case contained limited information. No reported relevant medical history, concomitant medication, ophthalmic

Table 71 Cases in the age group 18-24 years in the EU/UK region

Patient ID/ Serious (Y/N)/ Medically confirmed (Y/N)	Age (years) / Gender (M/F)	Country of origin	Verbatim (AE Preferred Term)	Co-reported events Reported	AE Outcome	Dose#/ TTO (days)	Concomitant meds/ Medical history/ Ocular history	WHO-UMC Causality Assessment/Comment
								history/assessment/investigation

AE Adverse Event, F Female, M Male, N No, TTO Time To Onset, UMC Uppsala Monitoring Centre, WHO World Health Organization

A cumulative search was conducted to identify any articles in embase, InsightMeme and PubMed using the terms retinal artery occlusion, retinal vein occlusion, retinal vein thrombosis, retinal vascular thrombosis, retinal blood vessel occlusion and retinal vascular occlusion. The search identified 7 literature articles. These articles were thoroughly reviewed. Two of the 7 articles (Sonawane et al 2021 and Kim et al 2021) have been discussed in literature case discussion. Two of the remaining 5 articles had relevant safety information to the topic of retinal vascular occlusion and COVID-19 VACCINE ASTRAZENECA.

In Park et al 2021, 23 eyes of 21 patients were included in the case series report and 8 of the patients received COVID-19 VACCINE ASTRAZENECA. Five of the 8 patients developed retinal vein occlusion (RVO). New or exacerbated (Retinal vein occlusion) RVO after vaccination was defined as a new vitreous or retinal hemorrhage developing with subjective symptom of decreased visual acuity within 28 days of vaccination that was clinically confirmed by at least three retinal specialists. Three of the 5 patients had hypertension (HTN), 1 patient had diabetes in addition to HTN and 1 patient had dyslipidaemia. The pre-existing ocular history was reported in 3 of these 5 patients which included vitrectomy for vitreous haemorrhage, vitrectomy with secondary IOL (intra-ocular lens) with scleral fixation and uveitis. The author suggested that these patients were more vulnerable to microvascular dysfunction and more likely to develop haemorrhagic complications after SARS-CoV-2 vaccination. Thus, the complications could be regarded as reactions in “at-risk” patients. Two of the 5 patients underwent anti-PF4 Ab tests; both were negative. Thus, the author concluded that an association between VITT and retinal/ sub macular haemorrhage in their cohort seemed unlikely. The author further stated that both the adenoviral and mRNA-based vaccines generated spike proteins; the trigger could be the spike proteins themselves or the immune reaction elicited by their presence. Molecular mimicry between the spike protein and a self-antigen could stimulate platelet activation and retinal haemorrhage.

AstraZeneca Comment: As stated by the authors, the patients in this case series report had pre-existing risk factors such as diabetes, hypertension and pre-existing ocular conditions to develop RVO. Most of the RVO developed unilaterally whereas most systemic drug-related retinal toxicity is bilateral. Thus the pathogenesis of retinal haemorrhages developing after SARS-CoV-2 vaccination does require further study.

Bolletta et al 2021 noted that arterial or venous retinal occlusion have both been described during or following COVID-19, which is thought to induce a systemic inflammatory response, endothelial dysfunction, and a hypercoagulative state, which predisposes patients to systemic thrombus formation. In their study there were five cases of RVO (one CRVO and four BRVO) and two of these patients received the COVID-19 VACCINE ASTRAZENECA. One of these 2 patients was affected by systemic comorbidity of systemic arterial hypertension (SAH). The authors commented that the complications could be related to the SARS-CoV-2 vaccines’ capacity to induce autoimmune manifestations or thromboembolic events. Additional

epidemiologic and clinical studies and longer follow-up of this cohort are needed to confirm the link between the COVID-19 vaccine and the recurrence or de novo development of uveitis and other ocular complications including RVO.

AstraZeneca Comment: The authors had noted that the study had limitations as it was of retrospective design and had relatively low number of cases. Conclusions cannot be drawn from the insufficient information provided for the two cases described in this article.

Summary

Of the 506 cases, there were no significant differences in the number of cases between gender and age groups. In 406 cases the dose information was unknown and in the remaining cases, majority of the cases (68) occurred after the second dose. Of the 506 cases reported, 261 were reported by healthcare professionals (medically confirmed) and were serious. One case was fatal which was confounded by risk factors and co-reported events.

Based on WHO-UMC causality classification, of the 506 cases, 324 cases were assessed as possible, 125 cases were unassessable as the TTO was not provided to make an assessment and 57 cases were unlikely as they occurred outside the 42 day risk window. Out of the 324 cases assessed as possible 183 cases had other confounding factors (other etiologies, or the vaccinees' medical history, comorbidities, concomitant medications, etc). The confounding factors included hypertension, diabetes, dyslipidaemia, atrial fibrillation, migraine, myocardial infarction, carotid artery thrombosis, hypercholesterolemia, smoking, glaucoma, history of central retinal vein occlusion, central retinal vein thrombosis, and uveitis.

An observed versus expected analysis of the cases overall and stratified by age in the EU, UK region showed that the observed cases were greater than expected (but the result was not significant) in the age group 18-24 years from the EEA and UK only group in both the 28 and 42 days risk window. Upon further analysis, 5 cases were identified in this category out of the 506 cases. Out of these cases 3 were assessed as possible by WHO-UMC causality classification and had limited information.

Retinal vascular occlusion could be caused by a systemic inflammatory response, endothelial dysfunction and a hypercoagulative state, which predisposed patients to systemic thrombus formation (Bolletta et al 2021). Park et al 2021 hypothesized on the mechanism of the SARS-CoV-2 vaccines' capacity to induce autoimmune manifestations or thromboembolic events. The authors postulated that the vaccine generates spike proteins; the trigger could be the spike proteins themselves or the immune reaction elicited by their presence and that the molecular mimicry between the spike protein and a self-antigen could stimulate platelet activation and retinal haemorrhage.

Conclusion

Based on a review of currently available information, it is the opinion of AstraZeneca that a reasonable possibility of a causal relationship between COVID-19 VACCINE ASTRAZENECA and Retinal vessel occlusion has not been established. No updates to the COVID-19 VACCINE ASTRAZENECA CDS or RMP are needed. AstraZeneca will continue to monitor events of retinal vessel occlusion through routine surveillance activities.

15.2.18 Sarcoidosis

AstraZeneca received the following request from PRAC in the AR for the 8th SSRs (review period: 01 October 2021 – 30 November 2021):

"Sarcoidosis: The MAH is requested to provide a cumulative review of sarcoidosis cases (HLT "Acute and chronic sarcoidosis") from all available sources, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccine. Depending on the results of this review, the MAH should also discuss the need for any potential amendment to the product information, as appropriate."

AstraZeneca's response to this request is provided below.

Review of Cases: Post-authorisation data

A cumulative search of the AstraZeneca global safety database through 28 December 2021 was conducted for reports of Sarcoidosis in association with the use of COVID-19 VACCINE ASTRAZENECA. The search included the following Preferred Terms (PT, MedDRA version 24.1) Sarcoidosis, Cardiac sarcoidosis, Cutaneous sarcoidosis, Liver sarcoidosis, Muscular sarcoidosis, Neurosarcoidosis, Ocular sarcoidosis, and Pulmonary sarcoidosis.

The search retrieved 54 cases with 60 AEs (54 serious and 6 non-serious events). One of the 54 cases was reported from a study (D8111C00004, post-authorization active surveillance of the Safety of COVID-19 Vaccines in the UK), and 3 cases from literature reports. The cases originated from the following countries: UK (35 cases), Germany (10 cases), France (3 cases), Netherlands (2 cases); and, in the remaining 4 cases, there was 1 case each from [redacted]

Of the 54 cases, 39 were consumer reports and, 15 were medically confirmed. The cases were reported in 32 females and 21 males; sex was not reported in the remaining 1 case. The median age was 49 years (range from 21 to 67 years). There were 2 cases with ages between 20 to 29 years, 4 cases with ages between 30 to 39 years, 18 cases with ages between 40 to 49 years, 13 cases with ages between 50 to 59 years, and 10 cases with ages between 60 to 69 years.

The cases reported 60 AEs (PTs) as follows: Sarcoidosis (48 events); Neurosarcoidosis (5 events); Pulmonary sarcoidosis (4 events); and 1 event each of Cardiac sarcoidosis, Cutaneous sarcoidosis, and Ocular sarcoidosis. Of the 54 cases, 4 reported more than 1 event.

The TTO for 32 of the 60 events was known, and of these 32 events, 25 had TTOs relative to the first dose and 7 had TTOs relative to the second dose. The TTOs from most recent dose to AE onset ranged from < 1 day to 151 days: 15 events had a TTO < 7 days; 6 events had a TTO of 7 to 21 days; 11 events had a TTO > 21 days; and, in the remaining 28 events, TTO was not reported. In 2 cases (Case IDs PPD), the vaccinees received an initial dose of COVID-19 VACCINE ASTRAZENECA followed by a dose of Moderna COVID-19 vaccine (Dose 2). In Case PPD , the vaccinee received the Moderna COVID-19 vaccine 75 days after the first dose of COVID-19 VACCINE ASTRAZENECA, and the AE onset was 76 days after the Moderna COVID-19 vaccine. Case ID PPD is summarized a few paragraphs below, where cases in literature are discussed.

The outcome of the 60 events at the time of reporting were as follows: 6 had recovered, 12 were recovering, 27 events were not recovered, and the outcome for the remaining 15 events was unknown. There were no cases with a fatal outcome.

Of the 54 cases, 28 had relevant medical history and/or relevant concomitant medications such as sarcoidosis, multiple sclerosis, breast cancer, steroid therapy, methotrexate, infliximab, mycophenolate mofetil as an immunosuppressive therapy, influenza vaccine, pneumococcal vaccine, Moderna COVID-19 vaccine, antiviral or antibiotics (which may suggest a possible infection) that could contribute to the event, and are possible confounders to an occurrence of sarcoidosis.

Twenty-four of the 54 cases did not provide sufficient information such as medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, and diagnostic and etiologic workup, which precluded a proper causal assessment.

The remaining 2 cases (PPD) were from 1 literature source (Rademacher et al 2021):

- PPD (Rademacher et al 2021) concerns a PPD -year-old PPD from PPD reported skin rash 3 weeks after PPD second SARS-CoV-2 vaccination. Reportedly, medical history was unremarkable, but details of concomitant medication (if any) were unknown. On an unknown date the patient received COVID-19 VACCINE ASTRAZENECA as the first dose 12 weeks earlier, followed by the second vaccination with an mRNA-based vaccine (CX-024414, Spikevax, Moderna, Inc., Cambridge, MA, US); dosing dates were not reported. PPD was present on the PPD , which had started 3 days after the 2nd vaccination and had spread to the PPD over the next 2 weeks. Eighteen days after receiving Spikevax, the patient reported immobilizing joint pain in both ankles. PPD denied fever or dyspnoea; a nasopharyngeal polymerase chain reaction test for SARS-CoV-2 RNA was negative. The patient experienced PPD

(preferred term: Sarcoidosis). On physical examination, both ankles were swollen and tender; otherwise, the physical examination was normal. Musculoskeletal ultrasound showed periarthritis with oedema and tendovaginitis of the surrounding tendon sheaths. Laboratory analysis revealed an elevated CRP of 28 mg/L (normal range: < 5 mg/L) and a negative result for procalcitonin. Other laboratory values, including ACE, were within the normal range. A chest radiography was unremarkable. Additional workup did not reveal any signs of other systemic sarcoidosis manifestations. PPD was treated with PPD at a dose of PPD as an outpatient. After 10 days of treatment, PPD reported persistence of arthralgia. Therapy with glucocorticoids was initiated (PPD with a tapering schedule), and PPD noticed an improvement of symptoms. At the 3-month follow-up after PPD initial presentation, the patient remained in clinical remission without any relapse of arthritis or skin manifestations. The following events were considered serious due to important medical event: PPD. The reporter considered the sarcoidosis to be related to treatment with Spikevax.

AstraZeneca Comment: The vaccinee experienced the events 12 weeks post COVID-19 VACCINE ASTRAZENECA and within a short time after second vaccination with mRNA vaccine. The authors also suggest a causal role of the mRNA vaccine ('cases of PPD starting 3 days and four weeks after vaccination').

- PPD (Rademacher et al 2021) concerns a PPD-year-old PPD from PPD, with no significant past medical history. On an unspecified date, PPD received the first SARS-CoV-2 vaccination with COVID-19 VACINE ASTRAZENECA without any relevant side effects. Seven weeks later PPD attended the emergency department with increasing ankle swelling and pain for 3 weeks. Other symptoms included an extensive reddish-violaceous rash on PPD with additional erythema nodosa on the PPD and undulating febrile temperatures and fatigue. A musculoskeletal ultrasound examination revealed bilateral ankle swelling with periarticular inflammation. The physical examination revealed no other relevant findings. The ESR was markedly elevated (80 mm in the first hour [NR < 15 mm]), the CRP was 220 mg/L. The soluble interleukin-2 receptor (sIL2-R) was slightly elevated (854 U/mL, [range: 223 to 710 U/mL]), angiotensin converting enzyme (ACE) levels were normal. Other laboratory analyses were normal. Due to elevated D-dimers, a chest computed tomography was performed with evidence of a segmental pulmonary artery embolism in the left upper segment artery. There were PPD consistent with sarcoidosis (PPD). The event was considered serious (hospitalized and important medical event) and the patient was treated with PPD at a dose of PPD and oral anticoagulation. Further workup did not reveal any other sarcoidosis-related organ manifestation. A lymph node biopsy was not performed,

given PPD typical presentation of PPD symptoms resolved quickly, and PPD was discharged after four days. At the four-month follow-up after PPD first presentation, no new or relapsing symptoms had occurred. The patient recovered on an unspecified date. The reporter considered the event of sarcoidosis to be related to treatment with COVID-19 VACCINE ASTRAZENECA.

AstraZeneca Comment: In this patient, the event occurred approximately after 4 weeks post-COVID-19 VACCINE ASTRAZENECA administration. However, there is limited information on patient's medical history and baseline condition, family history, concomitant medications, the patient's lifestyle and occupation that precluded a proper causality assessment. As per the authors, a coincidental seasonal effect could not be ruled out.

In summary, there were no index cases or any new signal identified from the review of case reports of sarcoidosis.

Review of Cases: Clinical Study Data:

A search was conducted in the AstraZeneca Clinical database for AE reports of Sarcoidosis following use of COVID-19 VACCINE ASTRAZENECA (AZD1222) reported from clinical studies (data cut-off of 07 December 2020 for the Oxford pooled studies and 30 July 2021 for Study D8110C00001). The search utilized MedDRA (MedDRA version 23.1) with the following Preferred Terms (PTs): Sarcoidosis; Cardiac sarcoidosis; Cutaneous sarcoidosis; Liver sarcoidosis; Muscular sarcoidosis; Neurosarcoidosis; Ocular sarcoidosis; Pulmonary sarcoidosis.

There were no case reports of Sarcoidosis from the Oxford pooled studies (COV001, COV002, COV003, and COV005), and no cases in the US study (D8110C00001).

Observed vs. Expected Analysis

A pragmatic literature search for articles on background rate for sarcoidosis revealed that most of the studies were conducted in the European Union (EU) and one study in Korea (Yoon et al 2018). The overall incidence of sarcoidosis varied between studies and was observed to be highest in Nordic countries and African Americans, ranging from 2.3 to 46 per 100000 person years (Arkema and Cozier 2018); the estimates from the Korea (Yoon et al 2018) were lower compared to other studies, thus representing a conservative approach. The incidence of sarcoidosis varies by age and sex, the Korean study presented data by age and sex. This is a population-based study using nationwide claims data from the Korean Health Insurance Review and Assessment Service. Exposure stratified by age was only available for the EU and the UK, and by gender only available for the UK; therefore, for these stratifications only EU/UK data was presented. Results of the observed versus expected (O/E) analysis for

Sarcoidosis are shown in Table 72. Based on the results, it can be concluded that the observed cases were significantly less than expected for overall, and for all age stratifications except in age group 20 to 29 and > 70 years, where the observed cases were less than expected (however, there were no observed cases in this age group).

Table 72 Observed versus Expected Analysis for Sarcoidosis

Age/ Gender Group[a]	Risk window (days)	BG Rate/1000000 Person-years[b]	Exposure[c]	Observed number of cases[d]	Expected number of cases[e]	O over E ratio (95% CI)	Conclusion
Overall all countries (TTO ≥ 7 days)	180	0.85	291626957	43	1221.62	0.04 (0.03-0.05)	Observed significantly < expected
Female 20-29 UK	180	0.27	1223509	0	1.63	0 (0-2.26)	Observed < expected
Female 30 – 39 UK	180	0.86	2096348	3	8.88	0.34 (0.07-0.99)	Observed significantly < expected
Female 40 – 49 UK	180	1.46	4974220	6	35.79	0.17 (0.06-0.36)	Observed significantly < expected
Female 50 – 59 UK	180	2.5	6319086	5	77.85	0.06 (0.02-0.15)	Observed significantly < expected
Female 60 – 69 UK	180	1.97	4859019	6	47.17	0.13 (0.05-0.28)	Observed significantly < expected
Female 70 – 79 UK	180	1.04	3562147	0	18.26	0 (0-0.2)	Observed significantly < expected
Female over 80 UK	180	0.11	1721795	0	0.93	0 (0-3.97)	Observed < expected
Male 20 – 29 UK	180	0.7	897434	0	3.1	0 (0-1.19)	Observed < expected
Male 30 – 39 UK	180	1.25	1582807	2	9.75	0.21 (0.02-0.74)	Observed significantly < expected
Male 40 – 49 UK	180	0.71	5220928	4	18.27	0.22 (0.06-0.56)	Observed significantly < expected

Table 72 Observed versus Expected Analysis for Sarcoidosis

Age/ Gender Group[a]	Risk window (days)	BG Rate/1000000 Person-years[b]	Exposure[c]	Observed number of cases[d]	Expected number of cases[e]	O over E ratio (95% CI)	Conclusion
Male 50 – 59 UK	180	0.76	6957211	4	26.06	0.15 (0.04-0.39)	Observed significantly < expected
Male 60 – 69 UK	180	1.02	4966917	2	24.97	0.08 (0.01-0.29)	Observed significantly < expected
Male 70 – 79 UK	180	0.75	3223317	0	11.91	0 (0-0.31)	Observed significantly < expected
Male over 80 UK	180	0.23	1042292	0	1.18	0 (0-0.31)	Observed < expected
18 – 49 EU+UK	180	0.9	11513485	27	51.07	0.53 (0.35-0.77)	Observed significantly < expected
50 – 59 EU+UK	180	1.62	6275981	13	50.11	0.26 (0.14-0.44)	Observed significantly < expected
60 – 69 EU+UK	180	1.52	18684704	10	139.97	0.07 (0.03-0.14)	Observed significantly < expected
70 – 79 EU+UK	180	0.92	8010180	0	36.32	0 (0-0.1)	Observed significantly < expected
80+ EU+UK	180	0.15	1094043	0	0.81	0 (0-4.55)	Observed < expected

CI Confidence interval; E, Expected; EU, European Union; O, Observed; TTO, time to onset; UK, United Kingdom.

[a] Including cases with unknown TTO.

[b] Background rates taken from Yoon et al 2018.

[c] Overall exposure cut-off is 02 January 2022. Stratified exposure cut-off is 27 December 2021.

[d] Cut off for observed number of cases is 28 December 2021.

[e] Cases reported within 0-7 days were excluded.

Literature

A search of Embase and InsightMeme databases was conducted for literature articles published between 01 January 2020 to 31 December 2021. The following search terms were utilized: Sarcoidosis, Boeck sarcoid, lymphogranulomatosis, Lofgren's syndrome in association with COVID-19 VACCINE ASTRAZENECA and other COVID-19 vaccines.

The literature search yielded a total of 15 articles. Of the 15 articles, 2 were considered as relevant for discussion as described below:

Watad et al 2021 presented an evaluation of immune-mediated diseases (IMD) flares or new disease onset within 28-days of SARS-CoV-2 vaccination at 5 large tertiary centres in countries with early vaccination adoption, 3 in Israel, one in UK, and one in the US. Authors assessed the pattern of disease expression in terms of autoimmune, autoinflammatory, or mixed disease phenotype and organ system affected, and evaluated their outcomes. Among the 27 cases, 21 (78%) had at least one underlying autoimmune/rheumatic disease prior the vaccination. Of the cases, 20/27 (75%) were mild to moderate in severity. Over 80% of cases had excellent resolution of inflammatory features, mostly with the use of corticosteroid therapy. Other immune-mediated conditions included idiopathic pericarditis (n = 2), neurosarcoidosis with small fibre neuropathy (n = 1), demyelination (n = 1), and myasthenia gravis (n = 2). Authors concluded that despite the high population exposure in the regions served by these centres, IMDs flares or onset temporally associated with SARS-CoV-2 vaccination appear rare; most are moderate in severity and responsive to therapy although some severe flares occurred.

Rademacher et al 2021 discussed 2 cases of sarcoidosis (Case IDs PPD and PPD) involving COVID-19 VACCINE ASTRAZENECA vaccination, which are both discussed above.

In conclusion, a review of the literature did not identify any safety concerns in association with Sarcoidosis and COVID-19 VACCINE ASTRAZENECA.

Discussion on Biological Plausibility and Possible Mechanisms

Sarcoidosis is an immunologically mediated disorder. Pathogenesis is believed to be a two-step process, requiring: (1) an initial exposure to an antigen that is presented to CD4+ T lymphocytes by antigen-presenting cells (human leukocyte antigen [HLA] class II molecules); and (2) an inflammatory milieu in which the antigen presentation can take place. Following antigen presentation, there is upregulation of the immune response, with activation of alveolar macrophages and dendritic cells, and development of memory for the causal antigen (sensitization) (Oliver and Zarnke 2021). Sarcoidosis is associated most strongly with HLA class II molecules on chromosome 6. The HLA-DRB1-11:01 allele is associated with increased risk for sarcoidosis in African-American and White subjects. HLA-DRB11-11:01 and occupational exposure to insecticides have been shown to interact in a positive manner to increase the risk for sarcoidosis ($p < 0.10$) and to increase risk for extrapulmonary sarcoidosis ($p < 0.05$), indicating the importance of both genetic and environmental factors (Oliver and Zarnke 2021).

No literature articles have been identified explaining the plausible mechanism of developing sarcoidosis after the use of COVID-19 VACCINE ASTRAZENECA. Also, no conclusive mechanism of action leading to Sarcoidosis after COVID-19 vaccination has been identified. Thus, to date the mechanism applicable to COVID-19 VACCINE ASTRAZENECA remains unclear.

Summary

AstraZeneca performed a cumulative evaluation of available data on Sarcoidosis from sources including COVID-19 VACCINE ASTRAZENECA clinical studies, post-authorisation case reports, the published literature, and quantitative review (O/E analysis). There were no AE reports of Sarcoidosis in the Oxford pooled studies and US studies. A review of the post-marketing cases did not identify any index case or a safety signal. The cases provided insufficient information which precluded a proper causality assessment, or were confounded by alternative aetiologies. The O/E analyses indicated that the number of observed cases of Sarcoidosis were significantly less, or less than expected cases. The review of relevant articles available in current literature did not identify any publications describing a causal association between Sarcoidosis and COVID-19 VACCINE ASTRAZENECA.

Conclusion

Based on the currently available data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between COVID-19 VACCINE ASTRAZENECA and Sarcoidosis. No updates to the COVID-19 VACCINE ASTRAZENECA labelling information or RMP are required. AstraZeneca will continue to monitor safety information for Sarcoidosis related events as part of routine safety surveillance.

15.2.19 Subacute thyroiditis

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021:

"The MAH is requested to comment on the signal from WHO-UMC on Subacute thyroiditis and to provide a cumulative review of cases reported with Vaxzevria. A discussion on the need to update the PI should be included."

AstraZeneca's response to this request is provided below.

Review of Cases

A cumulative review of the AstraZeneca global safety database through 28 December 2021 using the PTs: Autoimmune thyroiditis, Immune- mediated thyroiditis, Silent thyroiditis,

Thyroiditis, Thyroiditis acute, and Thyroiditis subacute reported with COVID-19 VACCINE ASTRAZENECA was completed. The search yielded 136 cases under all above mentioned PTs.

Of the 136 case reports, only a small number (37, 27%) were medically confirmed, with the remaining 99 (73%) being consumer reports. For details on all these cases, please refer to the Appendix 16 linked to this report, where all Serious cases are included and also all medically confirmed cases.

Vaccinee age was reported in 126 cases and an age distribution is provided in Table 73 below.

Table 73 Age Distribution of Vaccinees Reporting Autoimmune Thyroiditis reported with COVID-19 VACCINE ASTRAZENECA through 28 December 2021 (n = 126 reports with known age).

Age Group	Number of Patients	Frequency of Patients (%)
<30 years	5	4%
30 – 39 years	12	10%
40 – 49 years	42	33%
50 – 59 years	37	29%
60 – 69 years	24	19%
≥70 years	6	5%

N Number.

Among all these events from the topic of Autoimmune Thyroiditis (total 136), 89 (65%) were considered serious. None resulted in a fatal outcome. Of the serious reports, 24 (18%) were medically confirmed.

Case outcome was reported for 125 cases with 67 (49%) as Not recovered, 18 (13%) as Recovered, 37 (27%) as Recovering, 3 (2%) as Recovered with sequelae. Case outcome was unknown among 11 cases out of the 136 total cases.

Among the 136 cases of autoimmune thyroiditis, 20 cases reported medical histories of diseases related to the thyroid such as: hypothyroidism, autoimmune thyroiditis, thyroiditis subacute, thyroid mass, among others.

In total for the 89 cases, 144 adverse events were reported with the following distribution among the PTs searched for the concept of autoimmune thyroiditis (Table 74).

Table 74 Distribution of adverse events and PTs reported among the concept of Autoimmune thyroiditis with COVID-19 VACCINE ASTRAZENECA through 28 December 2021.

Adverse Event (PT)	Total Number of Events	Total Number of Serious Events	Total Number of Non-Serious Events
Autoimmune thyroiditis	36	24	12
Thyroiditis	46	31	15
Thyroiditis acute	18	15	3
Thyroiditis subacute	44	19	25

Time to onset was available in 92 of the 136 reports with the following distribution: under 1 day: 25 reports (18%), 2 – 5 days: 23 reports (17%), 6 – 9 days: 8 reports (6%), 10 – 15 days: 5 reports (4%), 16 – 20 days: 6 reports (4%), 21 – 30 days: 14 reports (10%), 31 – 60 days: 8 reports (6%), and >60 days: 3 reports (2%).

A total of 89 case reports of the concept of autoimmune thyroiditis with COVID-19 VACCINE ASTRAZENECA were serious, of these 24 were medically confirmed. A tabulation containing details, including patient demographics, time to onset, outcome, medical history and concomitant medications for the serious cases of Autoimmune Thyroiditis with COVID-19 VACCINE ASTRAZENECA has been provided in Appendix 16.

A total of 70 reports of serious cases were reported in women. A total of 37 reports among serious cases were reported in female patients with less than 50 years of age and the remaining 33 cases in female patients with more than 50 years of age. Only 19 serious cases were reported in males.

Of the 89 serious reports, outcome was reported in 86 reports as follows: 46 (53%) were reported as Not recovered, 11 (13%) were reported as Recovered, 27 (31%) were reported as Recovering and the remaining 2 (2%) were reported as Recovered with sequelae.

A total of 47 reports of Autoimmune thyroiditis cases with COVID-19 VACCINE ASTRAZENECA were non-serious.

From the non-serious reports 38 were reported in women in total, where age was reported in 20 cases in women less than 50 years old, and 16 cases reported in women older than 50 years of age.

There are 13 medically confirmed cases among non-serious reports. For details on these cases please refer to Appendix 20 where all medically confirmed cases are included.

Of the 47 Non-serious cases outcome was reported in 39 reports as follows: 21 (53%) were reported as Not recovered, 7 (18%) were reported as Recovered, 10 (26%) were reported as Recovering and the remaining 1 (3%) were reported as Recovered with sequelae.

Among all cases reporting any PT for the concept of Autoimmune Thyroiditis (total 136 cases), the events were reported after Dose 1 in 76 vaccinees, after Dose 2 in 19 vaccinees, and reported after an unknown dose in 41 vaccinees. No trend was observed.

Observed vs. Expected Analysis

An O/E analysis of autoimmune thyroiditis is provided in below Table 75 using 42, 180 and 236 day risk windows. The background incidence rate (IR) was based on McGrogan et al 2008. The later risk window of 236 days was used to account for vaccination post day 56 of initial or second dose of COVID-19 VACCINE ASTRAZENECA. The analyses showed that the observed number of cases were significantly less than expected for all risk windows including and excluding cases with known TTO.

Table 75 Observed versus Expected Analysis for Autoimmune thyroidits

Medical Concept	Risk Window (days)	BG rate/100,000 person years	Exposure	Observed cases	Expected cases	Observed over Expected ratio (CI 95%)	Conclusion
Autoimmune thyroiditis	42	80	291626957	84	26827.84	0 (0 - 0)	Observed significantly < expected
Autoimmune thyroiditis (including unknown TTO)	42	80	291626957	126	26827.84	0 (0 - 0.01)	Observed significantly < expected
Autoimmune thyroiditis	180	80	291626957	93	114976.44	0 (0 - 0)	Observed significantly < expected
Autoimmune thyroiditis (including unknown TTO)	180	80	291626957	135	114976.44	0 (0 - 0)	Observed significantly < expected
Autoimmune thyroiditis (Extended RW)	236	80	291626957	93	150746.89	0 (0 - 0)	Observed significantly < expected

Table 75 Observed versus Expected Analysis for Autoimmune thyroidits

Medical Concept	Risk Window (days)	BG rate/100,000 person years	Exposure	Observed cases	Expected cases	Observed over Expected ratio (CI 95%)	Conclusion
Autoimmune thyroiditis (Extended RW + Unk TTO)	236	80	291626957	135	150746.89	0 (0 - 0)	Observed significantly < expected

BG Background, CI Confidence Interval, RW Risk Window, TTO Time to Onset, Unk Unknown.

Summary

Most of the cases reported with these PTs lacked information or laboratory results and no trend was seen. Only 136 cases have being reported cumulatively with all these PTs "Autoimmune Thyroiditis, Immune- mediated Thyroiditis, Silent thyroiditis, Thyroiditis, Thyroiditis Acute, and Thyroiditis subacute". Considering the exposure of this vaccine this reporting rate is very low and below the expected rates in the background population. An observed to expected analysis done for this topic confirms this finding. Most of the case are reported among patients between 40 and 60 years of age and mainly in female, matching the demographic presentation of this disease in the overall population. Regarding time to onset no trend was seen among the cases reported, with 18 % of the cases reported within a day of vaccination and 17 % of cases reported within 2 till 5 days post vaccination. Only 16 cases were reported with the second dose, the rest was mainly with the first dose or an unknown dose. No rechallenge was observed.

Conclusion

Based on the review of the cumulative data, it is AstraZeneca's view that there is no evidence currently to conclude that the reported cases of Autoimmune thyroiditis, can be causality related to vaccination with COVID-19 VACCINE ASTRAZENECA.

In conclusion, the company does not consider that an update to the COVID-19 VACCINE ASTRAZENECA CDS or RMP are needed.

15.2.20 Tinnitus

Requests

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

"The MAH should continue the close monitoring of tinnitus and provide a refined analysis of medically confirmed cases in the next PSUR which should include: time to onset, duration of the symptoms, seriousness criteria, detailed description of the cases including medical history and causality assessment. Additionally the MAH is requested to present data from clinical studies, and medical literature including plausible mechanism of action."

In addition, the Committee for Medicinal Products for Human Use (CHMP) Rapporteur for the Study D8110C0001 Type II Variation (reference Procedure Number: EMEA/H/C/005675/II/0026) has requested a cumulative review of tinnitus in the PSUR.

AstraZeneca's response to these requests is provided below.

Review of Cases – Post-Authorisation Data

A search of the global patient safety database was conducted for cumulative adverse event data (from 29 December 2020 up to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PT 'Tinnitus' under MedDRA (version 24.1) in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified a total of 6731 cases (6598 spontaneous, 133 non-interventional/post-market study, no case from literature). Out of 6731 cases, 3378(50.2%) cases were reported serious and 3353(49.8%) cases were non-serious, 577(8.6%) were medically confirmed and 6154(91.4%) were consumer reports.

Out of 6731 cases, there were 4166(61.9%) for females, 2299(34.2%) for males and 266(4.0%) of unknown gender. The age was reported in 5922(88.0%) cases and both the mean and median age was 51.5 years.

For the 6731 cases, the reported event outcomes were as follows: 1 with fatal outcome, 4469(66.4%) not recovered, 744(11.1%) recovered, 101(1.5%) recovered with sequelae, 743(11.0%) recovering and 673(10.0%) with unknown outcome.

Fatal case PPD -year-old PPD was reported to have experienced tinnitus on day 2 after 2nd dose of COVID-19 VACCINE ASTRAZENECA and reportedly died due to subarachnoid haemorrhage 3 days after vaccination. The reported medical history of obstructive hydrocephalus, headache and hypertension are confounding factors for tinnitus. Limited information was available regarding etiologic and diagnostic work up. Autopsy details were not provided.

Amongst 845 cases with reported outcome recovered or recovered with sequelae, the AE duration was reported in 427 cases. For 356 (83.4%) cases the AE resolved within 7 days and for 71 (16.6%) cases the AE resolved after 7 days.

Amongst 6731 cases, time-to-onset (TTO) was reported for 5012(74.5%) cases, out of which 4005(79.9%) were reported in ≤ 7 days and 3347(66.8%) in ≤ 3 days as shown in Table 76. No particular chronology trend was seen in the remaining few AEs reported with a latency beyond 7 days. In 6192 cases the event was reported after the first dose, in 370 cases reported after the second dose, in 9 cases reported after both doses and in 3 cases reported after booster dose of COVID-19 VACCINE ASTRAZENECA and for 157 cases dose information was unknown.

Table 76 TTO for Cumulative Tinnitus Cases (From First Dose/Second Dose/Third Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	Percentage (%)
0 under 1 days	1227	51	3			19.0
1 day	1193	57	1			18.6
2 day	474	40	1			7.7
3 day	282	18				4.5
4 day	189	22		1		3.1
5 day	141	19				2.4
6 day	104	5				1.6
7 day	163	12	1	1		2.6
8-14 days	393	35	3		1	6.4
15-28 days	282	30				4.6
>28 days	227	36				3.9
Unknown	1517	44	1	1	156	25.5

TTO Time to Onset.

The most common co-reported AEs with the PT of ‘Tinnitus’ are shown in Table 77.

Table 77 Distribution of most frequently co-reported AEs in cases reporting Tinnitus, cumulatively

Adverse events	Number	Percentage (%)
Tinnitus	6731	-
Headache	2425	36.0
Fatigue	1416	21.0
Dizziness	1315	19.5
Pyrexia	1195	17.8
Nausea	994	14.8
Chills	936	13.9
Myalgia	747	11.1
Arthralgia	613	9.1
Malaise	507	7.5
Pain In Extremity	450	6.7

Amongst 6731 cases, the medical history was reported in 3401(50.5%) cases and the most common medical histories (majority) in descending order were tinnitus, suspected COVID-19, asthma, hypertension etc., which could also possibly explain the current event of tinnitus.

Rechallenge Cases

In 10 out of 6731 cases, the patient experienced tinnitus after 1st dose, and a recurrence or worsening of tinnitus with second dose of vaccination was reported PPD). The sources of the cases were consumer via regulatory authority. None of the cases reported any information on otolaryngology examination. The co-reported symptoms as were sensation of blocked sinuses, headache, sore throat, lymphadenopathy, pyrexia, muscle spasms, palpitations, unspecified systemic symptoms.

Possible confounders were identified in 8 out of 10 cases such as concomitant use of PPD ; arrhythmia in the backdrop of medical history of tinnitus and stoppage of beta-blockers (PPD); concomitant PPD in the backdrop of medical

history of tinnitus (PPD); multiple allergies like hay fever, asthma (PPD); medical history of tinnitus (PPD); multiple allergies and abscess jaw (PPD); concomitant beta 2 agonist medication in backdrop of palpitations and pulsatile tinnitus (PPD). Overall, there was insufficient information on start dates and any action taken with the concomitant medications and cause of pre-existing tinnitus. In two cases (PPD), there was insufficient information on medical history and concomitant medications for a comprehensive causal assessment.

In summary, on review of cases reporting tinnitus after 1st dose, and recurrence or worsening of tinnitus after 2nd dose, although possible confounder were identified in majority of cases (8 out of 10), a comprehensive causal attribution of other disease and drugs was not possible due to insufficient information on start dates and any action taken with the concomitant medications and cause of pre-existing tinnitus.

A summary table with details for the 577 medically confirmed cases is included in Appendix 13. Amongst these 577 medically confirmed cases, 194 (33.6%) were reported as serious and 384 (66.6%) were reported as non-serious. 393 (68.1%) cases for females, 172 (29.8%) cases for males and 12 (2.1%) cases with unknown gender. The age was reported in 526 (91.0%) cases and both the mean and median age was 49.5 years.

For the 194 serious AEs, the seriousness criteria were as follows: 1 AE reported as fatal, 4 AEs reported as life threatening, 28 AEs requiring hospitalisation, 74 AEs reportedly resulting in disability and 107 AEs reported as medically important.

For the 577 cases, the reported event outcomes were as follows: 1 with fatal outcome, 260(45.1%) not recovered, 122(11.1%) recovered, 11(1.9%) recovered with sequelae, 97(16.8%) recovering and 86 (14.9%) with unknown outcome. The details of the case (PPD) with fatal outcome was detailed in the section above.

Amongst 133 cases with outcome reported as recovered or recovered with sequelae, the AE duration was reported in 65 cases. For 49(75.4%) cases the AE reportedly resolved within 7 days and for 16(24.6) cases the AE was reported as resolved after 7 days.

Amongst 577 cases, time-to-onset (TTO) was reported for 471(81.6%) cases, out of which 391(83.0%) were reported in ≤ 7 days and 333(70.7%) in ≤ 3 days as shown in Table 78. No particular chronology trend was seen in the remaining few AEs reported with a latency beyond 7 days. In 545 cases the event was reported after the first dose, in 19 cases reported after the second dose, in 1 case reported after both doses and in 1 case reported after booster dose of COVID-19 VACCINE ASTRAZENECA and for 11 cases dose information was unknown.

Table 78 TTO for Medically Confirmed Tinnitus Cases (From First Dose/Second Dose/Third Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	Percentage (%)
0 under 1 days	132	1	1			23.2
1 day	122	4				21.8
2 day	46	3				8.5
3 day	24					4.2
4 day	14	1		1		2.8
5 day	13					2.3
6 day	11					1.9
7 day	16	1	1			3.1
8-14 days	25	1				4.5
15-28 days	26	2				4.9
>28 days	24	2				4.5
Unknown	92	3			11	18.4

TTO Time to Onset.

The most common co-reported AEs with the PT of 'Tinnitus' are shown in Table 79.

Table 79 Distribution of most frequently co-reported AEs in Medically Confirmed Tinnitus Cases

Adverse events	Number	Percentage (%)
Tinnitus	577	-
Headache	210	36.4
Pyrexia	121	21.0

Table 79 Distribution of most frequently co-reported AEs in Medically Confirmed Tinnitus Cases

Adverse events	Number	Percentage (%)
Fatigue	103	17.9
Dizziness	99	17.2
Nausea	96	16.6
Myalgia	81	14.0
Chills	70	12.1
Arthralgia	53	9.2
Malaise	50	8.7
Paraesthesia	41	7.1

AE Adverse Event.

Amongst 577 cases, 247 cases had relevant medical history and concomitant medications as risk factors. These were grouped into the following categories and most frequent confounders were:

Medical history:

- Pre-existing tinnitus (47 cases),
- Chronic condition (migraine/ headache/asthma/diabetes mellitus/alcohol abuse/tobacco user/hypertension/fibromyalgia/hypothyroidism/goitre/anaemia/thyroid mass/respiratory tract infection/spondyloarthropathy/polyneuropathy/basedow's disease/systemic lupus erythematosus/psoriasis/rheumatoid arthritis/multiple sclerosis/autoimmune thyroiditis - 87 cases),
- COVID-19 (32 cases),
- Allergies (33 cases),
- Anxiety and depression (13 cases),

- Other ear pathology (ear discomfort/excessive cerumen production/otitis media /hypoacusis/vestibular disorder/tympanic membrane perforation/acoustic neuroma - 12 cases),

- Cardiac pathology (myocardial ischaemia/catheterisation cardiac/cardiac failure chronic/myocardial infarction/cardiac pacemaker insertion/pericarditis/tachycardia/cardiovascular disorder/sinus tachycardia/aortic valve disease - 11 cases),

- Cancer (breast cancer/cervix neoplasm/colon cancer/leukaemia/neoplasm malignant - 7 cases).

Concomitant Medications:

- Anti-depressant medications (citalopram/sertraline/amitriptyline/fluoxetine/sertraline tablet/escitalopram/venlafaxine hydrochloride/duloxetine/mianserin/quetiapine/doxepin/ trazodone - 32 cases),

- Anti-Allergy drug (cetirizine/montelukast/salmeterol and fluticasone/fexofenadine/cyclizine/ranitidine/terbinafine/desloratadine/azelastine/famotidine/lordestin/prochlorperazine maleate/fluticasone & azelastine/dextroamphetamine - 23 cases),

- NSAIDs (naproxen/diclofenac sodium/ibuprofen/acetylsalicylic acid/celecoxib/acetaminophen - 19 cases),

- Antihypertensive drug (timolol/travoprost/tadalafil/prestarium/amlodipine/ramipril/tramadol/hydrochlorothiazide/lisinopril/perindopril/enalapril/indapamide - 13 cases),

- Antibiotics (azithromycin/amoxicillin/lymecycline/chloramphenicol/cefalexin/clavulanic acid - 9 cases)

AstraZeneca assessed the 577 medically confirmed cases according to WHO-UMC criteria using a risk window of 0-28 days. The 28 day risk window for tinnitus was selected based on the article from Carol Liu et al 2020, where the analysis on sensorineural deafness was performed during the 14 days prior to onset of hearing loss. Secondary analyses using risk intervals of days 1 to 28 and days 15 to 28 after vaccination were also evaluated. Out of a total of 577 medically confirmed cases, 106 cases did not have information on TTO and the remaining 471 cases had information on TTO.

26 cases were considered to be outside the risk window for COVID-19 VACCINE ASTRAZENECA and thereby considered as not reasonably related (TTO above 28 days).

445 cases were identified within risk window of 0-28 days and WHO-UMC causality was considered as possible.

Out of 445 possible cases, 227 cases did not have information on medical history, concomitant medication, corrective therapy, event outcome for a comprehensive causal assessment. In 218 cases, cases were confounded by medical history (such as pre-existing tinnitus, migraine, headache, asthma, diabetes mellitus, hypertension, fibromyalgia, hypothyroidism, thyroid dysfunction, anaemia, respiratory tract infection, spondyloarthropathy, polyneuropathy, autoimmune diseases, COVID-19, allergies, anxiety and depression, pre-existing ear pathologies, cardiovascular disorders, cancer etc) or concomitant medications (such as diuretics, anti-depressants, antibiotics, NSAIDS, anti-allergy medications, beta-blockers, calcium channel blockers) known to be associated with tinnitus.

Review of Cases – Clinical Data

In Study D8110C00001 as of the data cut-off 05 March 2021, a total of 29 participants with 30 events experienced a PT of Tinnitus: 27 events in the AZD1222 group and 3 in the placebo group. Randomization ratio was 2:1 (AZD1222; placebo). All were reported as non-serious.

The total number of participants (safety analysis set) were: AZD1222 = 21587, Placebo = 10792.

All of the 30 events were reported in participants from the US. Age range was from 37 to 68 years with a median age of 52.5 years. Of the 29 participants, 66% (19/29) were males and 34% (10/29) were females.

Of the 30 PTs of Tinnitus, 17 recovered/resolved, 1 was recovering, and 12 had not recovered.

Time from the start of AZD1222/placebo to AE onset (TTO) was as follows for TTO (dose 1): 1 day for 5 events; > 1 day to 1 week for 6 events; > 1 week to 1 month for 11 events; > 1month to 3 months for 8 events. Of the 13 events in which the event onset was after the second dose, the TTO (dose 2) was as follows: 1 day for 2 events; > 1 day to 1 week for 6 events; > 1 week to 1 month for 5 events.

All of the study participants, both in the AZD1222 and placebo groups, had contributory medical history/risk factors and/or concomitant medication confounders (eg, smoking, diabetes mellitus, hypertension, hyperlipidaemia and concomitant use of non-steroidal anti-inflammatory drugs, diuretics, cholesterol lowering agents and antidepressants).

Details of both related and unrelated events of Tinnitus. There were 10 cases reported as related by the investigator: 9 were confounded by medical history/risk factors or concomitant medications; the remaining 1 case had limited information to make an assessment. The same trend was observed in assessment of the unrelated cases. All of which were confounded by medical history/ risk factors or concomitant medications.

In Study D8110C00001 with the data cut-off of 30 July 2021, a total of 1 additional participant was reported to have experienced a PT of non-serious Tinnitus. This participant was in the AZD1222 group.

Observed versus Expected Analysis

An O/E analysis of tinnitus is provided in Table 80 below. The background incidence rate (IR) was based on Stohler et al 2019, the authors used Clinical Practice Research Datalink (CPRD), to calculate the IRs of first-time diagnosed tinnitus in an adult population between 2000 and 2016. Observed events were significantly less than the expected events using the risk window (RW) of 14 and 28 days and also including events with unknown TTO. Cumulative exposure (doses administered) up to 02 January 2022 was 291626957 doses.

Table 80 Observed Versus Expected Analyses for Tinnitus Cases

Adverse Events	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
Tinnitus within 14 days excluding unknown TTO	14	250	291626957	4434	27945.66	0.16 (0.15 - 0.16)	Observed significantly < expected
Tinnitus within 14 days including unknown TTO	14	250	291626957	6155	27945.66	0.22 (0.21 - 0.23)	Observed significantly < expected
Tinnitus within 28 days excluding unknown TTO	28	250	291626957	4746	55891.32	0.08 (0.08 - 0.09)	Observed significantly < expected

Table 80 Observed Versus Expected Analyses for Tinnitus Cases

Adverse Events	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
Tinnitus within 28 days including unknown TTO	28	250	291626957	6467	55891.32	0.12 (0.11 - 0.12)	Observed significantly < expected

BG Background; CI Confidence Interval; TTO Time To Onset.

Literature

As requested by PRAC, AstraZeneca completed a search of the literature to identify any articles in Embase, InsightMeme, and PubMed published from 29 December 2020 through 28 December 2021 identifying literature including potential mechanisms of action leading to tinnitus with COVID-19 VACCINE ASTRAZENECA.

The search yielded 9 articles, which were reviewed in detail, however none of the articles presented relevant information relating to this topic or conclusive mechanisms of action leading to tinnitus after ASTRAZENECA COVID-19 vaccination.

Summary

A total of 6731 reports of tinnitus have been cumulatively received with COVID-19 VACCINE ASTRAZENECA through 28 December 2021. The majority (61.9%) of cases were in females, and the mean age was 51.5 years. Of 6731 cases, in 6192 cases the event was reported after the first dose, and in 370 cases the event was reported after the second dose. 50.2% of cases were serious. One case had a fatal outcome (cause of death was subarachnoid haemorrhage). There were 577 medically confirmed cases of which 194 were serious. Amongst 577 cases, 445 cases were identified within risk window of 0-28 days and WHO-UMC causality was considered as possible. Out of 445 possible cases, 227 cases did not have information on medical history, concomitant medication, corrective therapy, event outcome for a comprehensive causal assessment. In 218 cases, strong confounding medical history was present. On review of cases reporting tinnitus after 1st dose, and recurrence or worsening of tinnitus after 2nd dose, possible confounders were identified in the majority of cases (8 out of 10). Observed events were significantly less than the expected events using the risk window (RW) of 14 and 28 days and also including events with unknown TTO. No conclusive mechanisms of action leading to tinnitus after ASTRAZENECA COVID-19 vaccination was identified.

Most cases were of short duration and occurred within the reactogenicity period. On review of cases from the AstraZeneca safety database, based on either insufficient case details (on medical history, concomitant medications, ocular examination) or presence of confounders (in roughly 50% of cases), a direct causal relationship of tinnitus to vaccine administration cannot be confirmed. Tinnitus is a symptom of several other medical events, and the events of tinnitus reported from the safety database were largely reported in association with other reactogenicity events which are already listed for COVID-19 VACCINE ASTRAZENECA and may be related to those events.

Conclusion

Based on the currently available data, AstraZeneca finds no evidence of a causal association between COVID-19 VACCINE ASTRAZENECA and tinnitus. No updates to the COVID-19 VACCINE ASTRAZENECA labelling information or RMP are required. AstraZeneca will continue to monitor tinnitus with COVID-19 VACCINE ASTRAZENECA as part of routine safety surveillance activities.

15.2.21 Vertigo

Requests

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021:

"The MAH is asked to continue a close monitoring of the reports related to vertigo after vaccination with Vaxzevria and to provide a refined analysis of medically confirmed cases in the next PSUR. The analysis should include : time to onset, duration of the symptoms, seriousness criteria, detailed description of the cases including medical history and causality assessment. Additionally the MAH is requested to present data from clinical studies, and medical literature including plausible mechanism of action."

The Committee for Medicinal Products for Human Use (CHMP) Rapporteur for the Study D8110C0001 Type II Variation (reference Procedure Number: EMEA/H/C/005675/II/0026) has requested a cumulative review of vertigo in the PSUR.

AstraZeneca's response to these requests is provided below.

Review of Cases – Post-Authorisation Data

A search of the global patient safety database was conducted for cumulative adverse event data (from 29 December 2020 up to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PT 'Vertigo' under MedDRA (version 24.1) in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified a total of 5595 cases (5482 spontaneous, 112 non-interventional/post-market study and 1 case from literature). Out of 5595 cases, 2670(47.7%) cases reported as were serious and 2925(52.3%) cases were reported as non-serious, 1360(24.3%) were medically confirmed and 4235(75.7%) were consumer reports.

Out of 5595 cases, there were 4052(72.4%) for females, 1390(24.8%) for males and 153(2.7%) of unknown gender. The age was reported in 5066(90.5%) cases and both the mean and median age was 55.6 years.

For the 5595 cases, the event reported outcomes were as follows: 3(0.1%) with fatal outcome, 1769(31.6%) not recovered, 1668(29.8%) recovered, 153(2.7%) recovered with sequelae, 1229(22.0%) recovering and 773(13.8%) with unknown outcome.

Fatal AEs of Vertigo

PPD : A PPD-year-old PPD patient was reported to have experienced vertigo 10 days post 1st dose vaccination with COVID-19 VACCINE ASTRAZENECA and reportedly died due to the events of nausea, headache and vertigo on an unspecified date. Limited information on medical history, etiologic and diagnostic work up as well on autopsy details.

PPD : A PPD-year-old PPD patient was reported to have experienced vertigo 1 day post 1st dose vaccination with COVID-19 VACCINE ASTRAZENECA and reportedly died due to the event of vertigo, headache, myalgia, fever, dyspnoea, hyperglycaemia and hypoxia on an unspecified date. The patient reportedly tested positive for COVID-19 which could possibly confound the fatality in this case. However, there was limited information on clinical course of the events, medical history, concomitant medication, etiologic and diagnostic work up as well on autopsy details.

PPD : A PPD-year-old PPD reportedly died due to acute disseminated encephalomyelitis, poorly responsive, vertigo, abdominal pain and fatigue at an unknown time after first dose of COVID-19 VACCINE ASTRAZENECA. Limited information was available in the report regarding medical history, concomitant medication, etiologic and diagnostic work up as well on autopsy details.

Amongst 1821 cases (recovered and recovered with sequelae), the AE duration was reported in 1096 cases. For 897(81.8%) cases the AE reportedly resolved within 7 days and for 199(18.2%) cases the AE reportedly resolved after 7 days.

Amongst 5595 cases, time-to-onset (TTO) was reported for 4239(75.8%) cases, out of which 3577(84.4%) were reported in ≤ 7 days and 3154(74.4%) in ≤ 3 days as shown in Table 81. No particular chronology trend was seen in the remaining AEs reported with a latency beyond 7 days. In 4866 cases the event was reported after the first dose, in 251 cases reported after the

second dose, in 4 cases reported after both doses and in 1 case reported after booster dose of COVID-19 VACCINE ASTRAZENECA and for 473 cases dose information was unknown.

Table 81 TTO for Cumulative Vertigo Cases (From First Dose/Second Dose/Third Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	Percentage %
00 under 1 days	1397	43	1		1	25.8
1 day	1079	24	1	1		19.7
2 day	350	20				6.6
3 day	226	11				4.2
4 day	140	13				2.7
5 day	99	4				1.8
6 day	52	8				1.1
7 day	93	13	1			1.9
8-14 days	255	23				5.0
15-28 days	196	23				3.9
>28 days	136	29				2.9
Unknown	843	40	1		472	24.2

TTO Time to Onset

The most common co-reported AEs with the PT of 'Vertigo' are shown in Table 82.

Table 82 Distribution of most frequently co-reported AEs in cases reporting Vertigo, cumulatively

Adverse events	Number	Percentage (%)
Vertigo	5595	-
Headache	2102	37.6
Nausea	1585	28.3

Table 82 Distribution of most frequently co-reported AEs in cases reporting Vertigo, cumulatively

Adverse events	Number	Percentage (%)
Pyrexia	1440	25.7
Dizziness	1320	23.6
Fatigue	1174	21.0
Chills	824	14.7
Myalgia	742	13.3
Vomiting	578	10.3
Arthralgia	544	9.7
Malaise	512	9.2

AE Adverse Event

Amongst 5595 cases, the medical history was reported in 2272 (41.0%) cases and the most common medical histories (majority) in descending order were suppressed lactation, hypertension, suspected COVID-19, vertigo, asthma, drug hypersensitivity etc. The medical history of hypertension, suspected COVID-19, vertigo, asthma, drug hypersensitivity could also possibly explain the current event of vertigo.

Rechallenges Cases

In 4 out of 5595 cases, vertigo after 1st dose, with a reported recurrence of vertigo with second dose of vaccination was reported (PPD). The sources of the cases were either consumer or spontaneous via regulatory authority. None of the cases reported any information on otolaryngology examination. The co-reported symptoms as were headache, nausea, tension headache, vertigo positional, pyrexia, syncope, tremor, tinnitus, mobility decreased, vomiting.

Possible confounders were identified in 2 out of 4 cases such as concomitant use of tamsulosin hydrochloride, vitex agnus-castus. Overall, there was insufficient information on start dates for vertigo, concomitant medications and relevant medical history for vertigo. In one case (PPD), there was insufficient information on medical history and concomitant medications for a comprehensive causal assessment.

In summary, on review of cases reporting vertigo after 1st dose, with a recurrence of vertigo with second dose, although possible confounders were identified in half of cases (2 out of 4), a comprehensive causal attribution of other disease and drugs was not possible due to insufficient information on start dates for vertigo and relevant medical history and concomitant medications.

Review of Medically Confirmed Vertigo Cases

A tabular summary of the 1360 medically confirmed cases of vertigo is provided in Appendix 14. Amongst 1360 medically confirmed cases, 379(27.9%) were serious and 981(72.1%) were non-serious. 966(71.0%) cases for females, 381(28.0%) cases for males and 13(1.0%) cases with unknown gender. The age was reported in 1253(92.1%) cases and both the mean and median age was 52.5 years.

For the 379 serious AE, the seriousness criteria were as follows: 3 AEs reported as fatal, 11 AEs with seriousness as life threatening, 108 AEs with seriousness as hospitalisation, 55 AEs with seriousness as disability and 230 AEs with seriousness as medically important.

Amongst 597 cases with outcome recovered or recovered with sequelae, the AE duration was reported in 406 cases. For 329(81.0%) cases the AE resolved within 7 days and for 77(19.0%) cases the AE resolved after 7 days.

Amongst 1360 cases, time-to-onset (TTO) was reported for 1217(89.5%) cases, out of which 1094(89.9%) were reported in ≤ 7 days and 998(82.0%) in ≤ 3 days as shown in Table 83. No particular chronology trend was seen in the remaining AEs reported with a latency beyond 7 days. In 1276 cases the event was reported after the first dose, in 45 cases reported after the second dose, in 1 case reported after both doses and for 38 cases dose information was unknown.

Table 83 TTO for Medically Confirmed Vertigo Cases (From First Dose/Second Dose/ Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	Percentage (%)
00 under 1 days	510	18				38.8
1 day	335	6				25.1
2 day	74	2				5.6
3 day	52	1				3.9
4 day	35	1				2.6
5 day	20	1				1.5

Table 83 TTO for Medically Confirmed Vertigo Cases (From First Dose/Second Dose/ Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	Percentage (%)
6 day	12	3				1.1
7 day	21	2	1			1.8
8-14 days	41	3				3.2
15-28 days	47	1				3.5
>28 days	27	4				2.3
Unknown	102	3			38	10.5

TTO Time To Onset.

The most common co-reported AEs with the PT of 'Vertigo' are shown in Table 84.

Table 84 Distribution of most frequently co-reported AEs in Medically Confirmed Vertigo Cases

Adverse events	Number	Percentage (%)
Vertigo	1360	-
Headache	521	38.3
Pyrexia	394	29.0
Nausea	322	23.7
Myalgia	200	14.7
Chills	164	12.1
Asthenia	164	12.1
Fatigue	157	11.5
Vomiting	136	10.0

Table 84 Distribution of most frequently co-reported AEs in Medically Confirmed Vertigo Cases

Adverse events	Number	Percentage (%)
Malaise	127	9.3
Influenza like illness	120	8.8

AE Adverse Event.

Amongst 1360 cases, 543 cases had relevant medical history and concomitant medications as risk factors. These were grouped into the following categories and most frequent confounders were:

Medical history: Hypertension (99), COVID-19 (39), diabetes mellitus (36), vertigo (25), hypothyroidism (20), obesity (20), tobacco user (16), migraine (13), thyroiditis (13), headache (12), autoimmune thyroiditis (12), atrial fibrillation (12), anxiety (10), breast cancer (10), hypercholesterolaemia (10), rheumatoid arthritis (9), anaemia (9), depression (9), dyslipidaemia (8), arteriosclerosis (7), fibromyalgia (7), multiple sclerosis (6), dizziness (6), thrombosis (5), disease risk factor (5), goitre (5), cerebrovascular accident (5), myocardial ischaemia (5), iron deficiency (5), prostate cancer (4), meniere's disease (4), acute myocardial infarction (4), cardiomyopathy (4), neoplasm malignant (4), carotid arteriosclerosis (4), thyroidectomy (4), neck pain (4), iron deficiency anaemia (4), heavy menstrual bleeding (3), tinnitus (3), cardiovascular disorder (3), rhinitis (3), coronary artery disease (3), vertigo positional (3), transient ischaemic attack (3), carotid artery stenosis (3), cervicobrachial syndrome (3), hyperlipidaemia (3), diplopia (2), influenza like illness (2), seizure (2), labyrinthitis (2), granulomatosis with polyangiitis (2), hyperthyroidism (2), tuberculosis (2), cerebrovascular disorder (2), mitral valve prolapse (2), epilepsy (2), herpes virus infection (2), cardiac assistance device user (2), alcoholic (2), cardiac disorder (2), pneumonia (2), spinal osteoarthritis (2), polymyalgia rheumatica (2), basal cell carcinoma (2), hypertensive heart disease (2) etc.

Concomitant Medications: Omeprazole (18), aspirin (10), clopidogrel (9), amlodipine (9), lansoprazole (7), gabapentin (6), betahistine (6), ramipril (6), gabapentin (6), perindopril (5), naproxen (5), ibuprofen (4), duloxetine (4), cardioaspirin (4), venlafaxine (4), valsartan + hydrochlorothiazide (3), cetirizine (3), pregabalin (3), losartan (3), hydrochlorothiazide (3), frovatriptan (2), candesartan (2), doxazosin (2), flecainide acetate (2), cinnarizine (2), levocetirizine (2), enalapril (2), lisinopril (2), doxazosin (2), timolol (2), methylprednisolone (2), topiramate (1), bumetanide (1), bimatoprost (1), methotrexate (1), sulfasalazine (1), amgevita (1), indapamide (1), olmesartan (1), fesoterodine fumarate (1), nifedipine (1), pregabalin (1), phenytoin sodium (1), infliximab (1), tolterodine tartrate (1), diclofenac (1),

beclometasone (1), ciprofloxacin (1), paracetamol and dihydrocodeine (1), erythromycin (1), levetiracetam (1), telmisartan (1), verapamil (1), alendronate sodium (1), lorazepam (1), abatacept (1), ketoprofene (1), olmesartan (1), modafinil (1), fluconazole (1), nitrofurantoin (1), trimethoprim (1), lithium (1), amiloride hydrochlorothiazide (1), olprezide (1), diazepam (1), mesigyna (1).

The WHO-UMC causality was assigned, with risk window/TTO defined as 0-28 days. The 28-day risk window for vertigo was selected based on the article from Carol Liu et al 2020, where the analysis on sensorineural deafness was performed during the 14 days prior to onset of hearing loss. Secondary analyses using risk intervals of days 1 to 28 and days 15 to 28 after vaccination were also evaluated. This article was used for the risk window for tinnitus, which is closely related/often associated with vertigo).

Out of a total of 1360 medically confirmed cases, 143 cases did not have information on TTO and the remaining 1217 cases had information on TTO.

31 cases were considered to be outside the risk window for COVID-19 VACCINE ASTRAZENECA and thereby considered as not reasonably related (TTO above 28 days).

1186 cases were identified within risk window of 0-28 days and WHO-UMC causality was considered as possible.

Out of 1186 possible cases, 806 cases did not have information on medical history, concomitant medication, corrective therapy, event outcome for a comprehensive causal assessment. In 366 cases, strong confounders medical history (such as pre-existing vertigo, cardiovascular disorder, neurological disorder, cancer, ear pathology, thyroid disorder, anxiety and depression, infections, anaemia, lifestyle issues, respiratory disorder, autoimmune disease etc) and multiple concomitant medications (such as diuretics, anti-depressants, antibiotics, NSAIDs, anti-allergy medications, beta-blockers, calcium channel blockers etc) known to be associated with vertigo.

In 9 cases received from regulatory sources, dizziness was wrongly coded to vertigo, however dizziness is listed for COVID-19 VACCINE ASTRAZENECA.

In 5 cases clinical features of vertigo occurred only after second dose. Although WHO-UMC causality is assessed as possible the event may be a coincidental finding.

Review of Cases – Clinical Data

In Study D8110C00001 as of the data cut-off 05 March 2021, a total of 40 participants (28 in the AZD1222-treated and 12 in the placebo-treated group) experienced 41 events of vertigo (29 in the AZD1222-treated and 12 in the placebo-treated group). Randomization ratio was

2:1 (AZD1222; placebo). All of the events were non-serious. There were no additional cases of vertigo reported with the 30 July 2021 data cut-off for Study D8110C00001

The total number of participants (safety analysis set) were: AZD1222 = 21587, Placebo = 10792

The events were reported in participants from the following countries: the US (n = 37), Peru (n = 2) and [redacted] (n = 1). Age range was from 19 to 83 years with a median age of 51 years. Of the 40 participants, 55% (22/40) were reported in females, and 45% (18/40) in males.

Of the 41 PTs of Vertigo, 33 (80%) had recovered/resolved, 2 (5%) were recovering and 6 (15%) were not recovered. There were no fatal events of Vertigo reported in this study.

Time from the start of AZD1222/placebo to AE onset (TTO) was as follows: same day for 3 events, > 1 day to 1 week for 11 events, > 1 week to 4 weeks for 13 events, > 4 weeks to 4 months for 14 events. No events were reported after 4 months.

Of the 28/40 (70%) participants who received AZD1222, 25/28 (89%) had contributory medical history/risk factors and/or concomitant medication confounders (such as medical history of vertigo, migraine/headache and use of concomitant medications that are labelled for Vertigo). The remaining 3 (11%) participants had limited information such as on medical history, concomitant medications, concurrent conditions and event details which precluded appropriate medical assessment of association of AZD1222 with vertigo.

Of the 12/40 (30%) participants who received placebo, 8/12 (67%) had contributory medical history/risk factors and/or concomitant medication confounders (such as medical history of vertigo, concurrent migraine/headache and use of concomitant medications that are labelled for Vertigo); and, the remaining 4 (33%) had limited information such as on medical history, concomitant medications, concurrent conditions and event details which precluded appropriate medical assessment of association of AZD1222 with vertigo.

In the current review of events of Vertigo reported from Study D8110C00001, none of the events were serious, led to withdrawal, discontinuation or death of a participant. Twenty-eight (28/40, 70%) of these participants received AZD1222 and 12/40 (30%) received placebo.

Of the 28/40 (70%) participants who received AZD1222, 16/28 (57%) were considered related and 12/28 (43%) were considered not related to AZD1222 by the investigator. In 25/28 (89%) of these participants, contributory risk factors such as medical history and concurrent conditions (such as medical history of vertigo, migraine and headache) or concomitant use of medications where vertigo is labelled for (such as duloxetine, propranolol, zolpidem and bupropion) were present. In the remaining 3 (11%) events, limited information such as on

medical history, concomitant medications, concurrent conditions and event details precluded appropriate medical assessment of association of AZD1222 with vertigo.

Observed versus Expected Analysis

An observed and expected analysis of vertigo is provided below (Table 85). The background IR was based on Stohler et al 2019, the authors used CPRD, and the IR was 1490.7 (1475.0 to 1506.4)/100,000 person-years. Observed events were significantly less than the expected events using the RW of 14 and 28 days and also including events with unknown TTO. Cumulative exposure (doses administered) up to 02 January 2022 was 291626957 doses.

Table 85 Observed Versus Expected Analyses for Vertigo Cases

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
Vertigo within 14 days excluding unknown TTO	14	1490.7	291626957	3853	166634.4	0.02 (0.02 - 0.02)	Observed significantly < expected
Vertigo within 14 days including unknown TTO	14	1490.7	291626957	5210	166634.4	0.03 (0.03 - 0.03)	Observed significantly < expected
Vertigo within 28 days excluding unknown TTO	28	1490.7	291626957	4073	333268.8	0.01 (0.01 - 0.01)	Observed significantly < expected
Vertigo within 28 days including unknown TTO	28	1490.7	291626957	5430	333268.8	0.02 (0.02 - 0.02)	Observed significantly < expected

AE Adverse Event, BG Background, CI Confidence Interval, TTO Time to Onset.

Literature

As requested by PRAC, AstraZeneca completed a search of the literature to identify any articles in Embase, InsightMeme, and PubMed published from 29 December 2020 through 28 December 2021 identifying literature including potential mechanisms of action leading to vertigo with COVID-19 VACCINE ASTRAZENECA. No articles were identified which presented relevant information relating to this topic or conclusive mechanisms of action leading to vertigo after ASTRAZENECA COVID-19 vaccination.

Summary

A total of 5595 cases of vertigo were cumulatively reported with COVID-19 VACCINE ASTRAZENECA through 28 December 2021. The majority (72.4%) of cases were in females, and the mean age was 55.6 years. Of 5595 cases, in 4866 cases the event was reported after the first dose, and in 251 cases the event was reported after the second dose. 47.7% of cases were serious. 3 cases had a fatal outcome (all containing limited information). There were 1360 medically confirmed cases of which 379 were serious. Amongst 1360 cases, 1186 cases were identified within risk window of 0-28 days and WHO-UMC causality was considered as possible. Out of 1186 possible cases, 806 cases did not have information on medical history, concomitant medication, corrective therapy, event outcome for a comprehensive causal assessment. In 366 cases, strong confounding medical history was present. On review of the 4 cases reporting vertigo after 1st dose, with a recurrence of vertigo with second dose, possible confounders were identified in half of the cases (2 out of 4). Observed events were significantly less than the expected events using the RW of 14 and 28 days and also including events with unknown TTO. No conclusive mechanisms of action leading to vertigo after ASTRAZENECA COVID-19 vaccination was identified.

Most cases were of short duration and occurred within the reactogenicity period. On review of cases from the AstraZeneca safety database, based on either insufficient case details (on medical history, concomitant medications, otitic or aural examination) or presence of confounders (in roughly 50% of cases), no significant trend in otitic, aural or thromboembolic cerebrovascular symptoms, a direct causal relationship of vertigo to vaccine administration cannot be confirmed. Vertigo is a symptom of several other medical events, and the events of vertigo reported from the safety database were largely reported in association with other reactogenicity events which are already listed for COVID-19 VACCINE ASTRAZENECA and may be related to those events.

Conclusion

Based on the currently available data, AstraZeneca finds no evidence of a causal association between COVID-19 VACCINE ASTRAZENECA and vertigo. No updates to the COVID-19 VACCINE ASTRAZENECA labelling information or RMP are required. AstraZeneca will continue to monitor vertigo with COVID-19 VACCINE ASTRAZENECA as part of routine safety surveillance activities.

15.2.22 Viral herpes infection

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

"The MAH should provide an updated cumulative review of cases of the most frequently reported PTs ie, Herpes zoster, and Oral herpes, discuss potential cases of rechallenge, discuss literature findings, explore potential mechanisms and discuss on the need to update the product information. The MAH is asked to make efforts to identify background rates of Herpes zoster and Oral herpes independently (ie from the literature), and to conduct the O/E analysis."

AstraZeneca's response to these requests is provided below.

Review of cases

A cumulative search through 28 December 2021 of the AstraZeneca Global Patient Safety Database was conducted for adverse event reports of viral herpes infection in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search strategy used PTs: Herpes zoster and Oral herpes under MedDRA (version 24.1). The search identified a total of 4774 cases (4668 spontaneous, 98 non-interventional/post-market study and 8 literature), reporting 4886 AEs as follows: Herpes zoster (3602) and Oral herpes (1284). Of 4774 cases, 2064 (43%) cases were reported as serious and 2710 (57%) cases were reported as non-serious, 833 (17%) were medically confirmed and 3941 (83%) were not medically confirmed. A listing of the 2064 serious cases of viral herpes infection is included in Appendix 21.

Of the 4774 cases, there were 3201 (67%) for females, 1437(30%) for males and 136 (3%) of unknown gender. Amongst 4774 cases, 1 case belongs to a PPD-year-old patient, the age range was 18 to 65 years in 3198 (67%) cases, in 1108 (23%) cases the age group was elderly (>65 years) and for the remaining 467 (10%) cases the age was not provided. Mean age was 56.7 years.

Amongst 2064 serious cases, 252 (12%) were medically confirmed and 1812 (88%) were not medically confirmed, 1429 (69%) for females, 562 (27%) for males and 73 (4%) of unknown gender. The age range was 18 to 65 years in 1420 (69%) cases, in 438 (21%) cases the age group was elderly (>65 years) and for the remaining 206 (10%) cases the age was not provided. The count of reported adverse events by preferred terms included Herpes zoster (1570) and Oral herpes (501).

For the 2064 serious cases, the event reported outcomes were as follows: 1073 (52%) were not recovered, 224 (11%) were recovered, 65 (3%) was recovered with sequelae, 641(31%) were recovering and 61 (3%) events were with unknown outcome.

Amongst 2064 serious cases, time-to-onset (TTO) was reported for 1618 cases and was unknown for 446. In 1573 cases events were reported after the first dose, in 428 cases events were reported after the second dose, in 1 case the event was reported after both the doses, in 6 cases the events were reported after booster dose and for 56 cases dose information was unknown (Table 86).

Table 86 TTO for Serious Herpes Zoster and Oral Herpes Cases (From First Dose/Second Dose/Third Dose/Dose Unknown)

Time to Onset (Days)	No of Cases (From First Dose)	No of Cases (From Second Dose)	No of Cases (From First and Second Dose)	No of Cases (From third Dose)	No of Cases (Dose Unknown)	%
00 Under 1 day	96	15	1			5.4
01 to 21 days	894	242		3		55.2
22 days and above	284	82		1		17.8
Unknown days (missing)	299	89		2	56	21.6

TTO Time To Onset.

Amongst 2064 serious cases, 915 cases had relevant reported medical histories and/or concomitant medications as confounding factors. These were grouped into the following categories and most frequent confounders were: herpes simplex/oral herpes/herpes zoster/varicella (423 cases), illness such as asthma, osteoporosis, inflammatory bowel disease, chronic kidney disease etc. (186 cases), COVID-19 (183), autoimmune disease such as multiple sclerosis, rheumatoid arthritis, Addison’s disease, Basedow's disease, autoimmune hypothyroidism, coeliac disease, vasculitis, lichen planus, immune thrombocytopenia, immune-mediated hepatitis, diabetes mellitus etc. (161 cases), steroid therapy (113 cases), immunodeficiency (67 cases), emotional stress/anxiety (58 cases), immunosuppression therapy (53 cases), cancer (51 cases), fatigue (39 cases), surgery (32 cases), infection (30 cases), injury (9 cases), organ transplant (5 cases) and HIV (3 cases).

WHO-UMC Causality Assessment

AstraZeneca performed WHO-UMC causality assessment using a risk window defined as 1-21 days. Out of a total of 2064 serious cases, 446 cases did not have information on TTO and remaining 1618 cases had information on TTO.

479 cases were considered to be outside the risk window for COVID-19 VACCINE ASTRAZENECA administration and herpes Psichogiou et al 2021 and thereby considered as not reasonably related (TTO less than 1 day and above 21 days).

Of the 2064 serious cases, AstraZeneca assigned WHO-UMC causality using a risk window defined as 1-21 days. A total of 1139 cases were identified within the risk window of 1-21 days. In 292 cases, TTO was less than 2 days with no reports of previous herpes infection or exposure and were considered to be temporarily implausible to vaccine administration in view of the known incubation period of the virus (CDC 2021 [B] and CDC 2021 [C]). After removal of these 292 cases, there were 847 cases within the risk window 1-21 days, and assessed by AstraZeneca as possible per WHO-UMC. Of these 847 cases, 500 cases did not have information on medical history and concomitant medication for a comprehensive causal assessment. Out of 847 cases, in 228 cases, strong confounders (such as immunodeficiency, autoimmune disease, HIV, cancer, organ transplant, infection, surgery, injury, concomitant immunosuppressants, steroid therapy etc.) were identified for herpes zoster and oral herpes.

Out of 1139 cases, there were 847 cases within the risk window 1-21 days. Of these 847 cases, 500 cases did not have information on medical history and concomitant medication for a comprehensive causal assessment. Out of 847 cases, in 228 cases, strong confounders (such as immunodeficiency, autoimmune disease, HIV, cancer, organ transplant, infection, surgery, injury, concomitant immunosuppressants, steroid therapy etc.) were identified for herpes zoster and oral herpes.

In 34 cases clinical features of herpes occurred only after second dose. Although AstraZeneca assessed these cases as possible according to WHO-UMC causality, the event may be a coincidental finding.

In 85 cases, a clear confounder was not identified, however due to insufficient information on clinical course, treatment taken and presence of virus/viremia it was not possible to make a comprehensive causal assessment. The majority of the 85 cases reported a medical history of suppressed lactation however the reason for suppression of lactation was unknown. It is possible that the mother had a medical history of herpes and was advised not to breastfeed.

Potential Cases of Rechallenge

One case (PPD), a PPD -year-old patient of an unknown gender, had a history of PPD . The patient received COVID-19 VACCINE ASTRAZENECA on PPD (first dose) and on PPD (second dose). On PPD and

on PPD, the patient was reported to have experienced oral herpes and herpes zoster respectively. The patient reportedly recovered from oral herpes, but the event of herpes zoster was reported as ongoing. The appearance of oral herpes on same day of vaccination is considered temporarily implausible. A latency of 101 days after the second dose is also considered temporarily implausible. Wide variations in the TTO between first dose and second dose excludes any particular etiopathology.

Also, none of the cases reported any information on correlation of clinical features with markers of presence of actual virus or viraemia or virus entering lytic or herpes in close contact (such as viral DNA PCR and any batch number for possible contaminations).

Observed versus Expected Analysis

The medical concept of herpes viral infections is not included in the ACCESS programme.

For both herpes zoster and oral herpes: For global and all age stratifications the observed number of cases was significantly lower than the expected number of cases (Table 87 and Table 88).

A pragmatic literature review was conducted in order to identify relevant articles to provide the most appropriate background rate for both herpes zoster, and oral herpes. One publication (James C et al 2020), a systematic review, provides estimated global incidence for HSV-1, responsible for oral herpes, and provides granularity across regions and age groups. This is the most comprehensive source to date.

Regarding herpes zoster, the incidence varied according to the studied population. Indeed, the incidence increases with age. The incidence rate selected from a European study (Johnson et al 2015) and official CDC website, is the most conservative one, reported in the general population in the US. The higher bound of the incidence rate selected is the average incidence in the 60+ population.

Table 87 Observed Versus Expected Analysis for Herpes Zoster Cases within 21 days

Concept (Herpes Zoster)	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All cases, all ages (RW 21)	21	340	291626957	1917	57009.15	0.03 (0.03 - 0.04)	Observed significantly < expected
All cases, all ages (RW 21+Unk)	21	340	291626957	2795	57009.15	0.05 (0.05 - 0.05)	Observed significantly < expected

Table 87 Observed Versus Expected Analysis for Herpes Zoster Cases within 21 days

Concept (Herpes Zoster)	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-54 (UK)	21	720	6634875	102	2746.65	0.04 (0.03 - 0.05)	Observed significantly < expected
55-59 (UK)	21	862	6641536	147	3291.65	0.04 (0.04 - 0.05)	Observed significantly < expected
60-64 (UK)	21	1021	5615191	133	3296.31	0.04 (0.03 - 0.05)	Observed significantly < expected
65-69 (UK)	21	1172	4210819	109	2837.48	0.04 (0.03 - 0.05)	Observed significantly < expected
70-74 (UK)	21	1287	4029078	53	2981.41	0.02 (0.01 - 0.02)	Observed significantly < expected
75-79 (UK)	21	1428	2756426	32	2263.15	0.01 (0.01 - 0.02)	Observed significantly < expected
80+ (UK)	21	1399	2764092	20	2223.35	0.01 (0.01 - 0.01)	Observed significantly < expected
50-59 (EU/UK)	21	790	19552392	411	8881.06	0.05 (0.04 - 0.05)	Observed significantly < expected
60-69 (EU/UK)	21	1090	28510714	682	17867.86	0.04 (0.04 - 0.04)	Observed significantly < expected
70-79 (EU/UK)	21	1360	14795684	241	11569.43	0.02 (0.02 - 0.02)	Observed significantly < expected
80+ (EU/UK)	21	1399	3858135	57	3103.37	0.02 (0.01 - 0.02)	Observed significantly < expected

BG Background; CI Confidence Interval; E Expected; EU European Union; O Observed; RW Risk Window; UK United Kingdom; Unk Unknown

Table 88 Observed Versus Expected Analysis for Oral Herpes Cases within 21 days

Concept (Oral Herpes)	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All cases, all ages (RW 21)	21	1700	291626957	942	285045.75	0 (0 - 0)	Observed significantly < expected
All cases, all ages (RW 21+Unk)	21	1700	291626957	1161	285045.75	0 (0 - 0)	Observed significantly < expected
15-19 Male (UK)	21	1900	88941	2	97.16	0.02 (0 - 0.07)	Observed significantly < expected
20-24 Male (UK)	21	1600	401538	4	369.39	0.01 (0 - 0.03)	Observed significantly < expected
25-29 Male (UK)	21	1400	495896	4	399.17	0.01 (0 - 0.03)	Observed significantly < expected
30-34 Male (UK)	21	1100	699000	7	442.09	0.02 (0.01 - 0.03)	Observed significantly < expected
35-39 Male (UK)	21	1000	883807	12	508.15	0.02 (0.01 - 0.04)	Observed significantly < expected
40-44 Male (UK)	21	800	2460200	21	1131.61	0.02 (0.01 - 0.03)	Observed significantly < expected
45-49 Male (UK)	21	700	2760728	17	1111.12	0.02 (0.01 - 0.02)	Observed significantly < expected
15-19 Female (UK)	21	1700	115825	1	113.21	0.01 (0 - 0.05)	Observed significantly < expected
20-24 Female (UK)	21	1100	545832	6	345.22	0.02 (0.01 - 0.04)	Observed significantly < expected
25-29 Female (UK)	21	700	677677	14	272.75	0.05 (0.03 - 0.09)	Observed significantly < expected

Table 88 Observed Versus Expected Analysis for Oral Herpes Cases within 21 days

Concept (Oral Herpes)	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
30-34 Female (UK)	21	500	945726	19	271.88	0.07 (0.04 - 0.11)	Observed significantly < expected
35-39 Female (UK)	21	300	1150622	34	198.47	0.17 (0.12 - 0.24)	Observed significantly < expected
40-44 Female (UK)	21	200	2382386	61	273.96	0.22 (0.17 - 0.29)	Observed significantly < expected
45-49 Female (UK)	21	100	2591834	62	149.02	0.42 (0.32 - 0.53)	Observed significantly < expected

BG Background; CI Confidence interval; E Expected; O Observed; RW Risk Window; UK United Kingdom; Unk Unknown

Based on the results of the observed versus expected analysis, it can be concluded that for both herpes zoster and oral herpes, for the global and all age stratifications, the observed number of cases was significantly lower than the expected number of cases.

Literature

As requested by PRAC, AstraZeneca completed a search of the literature to identify any articles in Embase, InsightMeme, and PubMed published from 29 December 2020 through 28 December 2021 identifying literature including potential mechanisms of action leading to viral herpes infection with COVID-19 vaccination. The search parameters have been included in Appendix 21 of this safety report.

The literature search yielded a total of 183 articles. Of the 183 articles, 2 were considered as relevant for discussion (based on strength of evidence) as the sample size was large and they had a comparison group. The remaining articles included case reports and case series without any comparison groups and hence the strength of evidence is considered as weak. Additionally, review of the case report and case series articles presented insufficient information (such as current or previous contact exposure to a herpes case, testing in partners, any evidence of virus lytic phase, any viral shedding, or documented systemic severity or any batch number for possible contaminations). These case reports and case series involving AstraZeneca vaccine are already databased within the Global Safety Database and are not discussed in this literature section.

- Barda et al 2021 Data from a health care organization database in Israel was evaluated for the safety of the BNT162b2 mRNA vaccine with vaccinated and control groups each included a mean of 884,828 persons. The author compared the incidence of a broad set of potential short- and medium-term adverse events among vaccinated persons with the incidence among matched unvaccinated persons. The authors concluded that vaccination was most strongly associated with an elevated risk of herpes zoster infection (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24.2). SARS-CoV-2 infection was not estimated to have a meaningful effect on the incidence of herpes zoster infection.

  AstraZeneca Comment: There are limitations to the study as mentioned by the author. These include persons in the study were not randomly assigned, the cohorts that were used to study the vaccine and infection effects were different in composition, the exclusion of certain populations (such as health care workers and persons residing in long-term care facilities), diagnoses that were recorded in out-of-network hospitals, which were delayed in being reported to the insurer, and the possibility that persons were more likely to increase their levels of clinical awareness, concern, or both after vaccination or SARS-CoV-2 infection, and thus they may be more likely to report or seek medical care for their symptoms, resulting in a spuriously increased incidence of the various adverse events in the vaccinated or infected groups. The incidence rate of herpes zoster in this study was approximately 0.3 per 1000 exposed persons which is low as compared to the reported incidence rate in Israel general population (3 cases per 1000 exposed persons) Weitzman et al 2021. Therefore there appears to be no absolute increase in herpes zoster infections with BNT162b2 mRNA vaccine. There was insufficient information on concomitant medications in the comparison group (SARS-CoV-2 infection), clinical features for herpes virus infection, etiological and diagnostic workup, and hence the apparent increase in incidence rate in herpes zoster with vaccination as compared to the comparison group cannot be comprehensively assessed. Moreover, there was no increase in (absolute or relative) in herpes simplex infection. In view of the limitations as described above AstraZeneca agrees with the author further studies will be needed to estimate the potential of long-term adverse events.

- Shasha et al 2022 A real-world study, an observational historical cohort study, assessed the possible association between BNT162b2 vaccination and several predefined clinical events in a cohort of vaccinees compared with a matched cohort of unvaccinated individuals. This study compared the rates of herpes zoster among vaccinated and unvaccinated individuals. Individuals ≥16 years vaccinated with at least one dose of BNT162b2 were eligible for this historical cohort study in a health maintenance organization insuring 1.2 million citizens. 151 versus 141 cases of herpes

zoster (RR 1.07, CI 0.85–1.35) was reported with no association found between vaccination and herpes zoster.

AstraZeneca Comment: On review of the article it is agreed that there are limitations to the study as per described by the author. This includes its observational design, for which the author tried to compensate with a large study cohort and a rigorous matching. While matching for age, sex, population sector, number of comorbidities and length of follow-up reduced possible confounders, it came at a cost of not including 41% of the eligible vaccinated individuals. Although the article has limitations of the observational design, the strengths of this article include the comparison group design for herpes zoster and being a large study.

From the PRAC PSUR assessment report 2 articles were suggested (Mohta et al 2021 and Iwanaga et al 2022) to be discussed and the details are below:

- Mohta et al 2021 A case series of herpes zoster within a week following COVID-19 vaccination (ChAdOx1 nCoV-19) in patients treated with cyclosporine was reported. Three cases who developed reactivation of recurrent herpes zoster following COVID-19 vaccination (recombinant ChAdOx1 nCoV-19 coronavirus vaccine also known as Covishield) was discussed. All patients were known cases of chronic spontaneous urticaria being treated with capsule cyclosporine for at least one month. The author recognises that it is not possible to establish a direct correlation between the vaccination and recurrence of herpes zoster as there was a strong clinical suspicion of iatrogenic immunosuppression due to cyclosporine in the cases which could be a major contributory factor.

  AstraZeneca Comment: A possible mechanism was also described within this article. The varicella zoster virus has a predilection for the peripheral nerves. Following a primary infection, it can lie in dormant in the dorsal root ganglia of the spinal cord for years, and get reactivated following any stressful event to the body, namely surgeries, high grade fever, prolonged illness, immunosuppression, vaccination, etc. The author had noted that a sudden resurgence of herpes zoster is being reported in COVID-19 infected individuals, even in the absence of any immunosuppression. The author has attributed this to the lymphopenia and CD4 T cell impairment induced by viraemia, thereby, vaccination induced cellular immune suppression and up regulation of alloreaction can play a role in triggering the reactivation of varicella zoster virus in the same way. Additionally, the cyclosporine induced T cell suppression could play a major contributory role in this reaction. This is a hypothesis by the author but there is no information on mechanism based studies linking viral herpes and COVID-19 vaccinations in general. On review of the article AstraZeneca agrees with the author's

conclusion regarding iatrogenic immunosuppression due to cyclosporine in the cases that it is a strong confounder to the cases.

- Iwanaga et al 2022 A literature review on herpes zoster infection following COVID-19 vaccines. Two cases of oral herpes zoster following the COVID-19 vaccine were described with respective clinical anatomy discussed. From a total of 399 cases that were identified the author reports the affected dermatomes mimicking the regular distribution of herpes zoster. It was further reported that some patients who had a history of varicella zoster virus vaccination had herpes zoster following the COVID-19 vaccination and two patients with oral herpes zoster following vaccination were also found to have involvement of the greater palatine nerve.

  AstraZeneca Comment: On review of the article the company confirms that more information (such as the patient's current status for concomitant medications) would be desired to make a clear causality agreement and at present there is limited information to the cases discussed. This is a narrative review without sufficient analysis presented by the authors for a comprehensive causality assessment.

Potential mechanism of action

The following article discusses a potential mechanism for viral herpes reactivation with Covid-19 vaccine administration:

- Burrows et al 2021 A possible mechanism of action could involve reactivation of the dormant virus within the CNS causing facial nerve inflammation or oedema after administration of the vaccine. A proposed mechanism of idiopathic facial nerve palsy suggests reactivation of latent herpes virus in a similar mechanism to Ramsey Hunt syndrome and the reactivation of the varicella zoster virus.

There were no articles confirming the latent virus switching to the lytic phase of replication or increase in viral shedding and testing new herpes infections in close contacts.

Summary

A total of 4774 cases of herpes zoster were cumulatively reported with COVID-19 VACCINE ASTRAZENECA through 28 December 2021. The majority (67%) of cases were in females, 67% of cases were in the age range 18 to 65 years. Mean age was 56.7 years.

Amongst 2064 serious cases, in 1573 cases, the events were reported after the first dose, in 428 cases the events were reported after the second dose, in 1 case the event was reported after both the doses, in 6 cases the events were reported after booster dose and for 56 cases dose information was unknown. No cases had a fatal outcome.

Of 2064 serious cases, the WHO-UMC causality was assigned, with risk window/TTO defined as 1-21 days. 1139 cases were identified within risk window of 1-21 days. In 292 cases, TTO was less than 2 days with no reports of previous herpes infection or exposure and were considered to be temporarily implausible to vaccine administration in view of the known incubation period of the virus. After removal of these 292 cases, there were 847 cases within the risk window 1-21 days, and assessed as possible per WHO-UMC. Of these 847 cases, 500 cases did not have information on medical history and concomitant medication for a comprehensive causal assessment. Out of 847 cases, in 228 cases, strong confounders were identified for herpes zoster and oral herpes.

In one rechallenge case a PPD-year-old patient with a history of PPD, experienced oral herpes after first dose, and herpes zoster after 2nd dose. The appearance of oral herpes on same day of vaccination was considered temporarily implausible with regards to association with AZD1222. A latency of 101 days after the second dose was also considered temporarily implausible. For both herpes zoster and oral herpes, for global and all age stratifications the observed number of cases was significantly lower than the expected number of cases.

Burrows et al 2021 proposed a possible mechanism of action which could involve reactivation of the dormant virus within the CNS causing facial nerve inflammation or oedema after administration of the vaccine. A proposed mechanism of idiopathic facial nerve palsy suggests reactivation of latent herpes virus in a similar mechanism to Ramsey Hunt syndrome and the reactivation of the varicella zoster virus. A further exploration of these mechanisms were not identified. Moreover, the same study had limited information on actual replication of virus or transmission of virus to possible close contacts. Also, no mechanism based study was identified. In summary, no conclusive mechanism could be identified.

In summary, although there were cases with information showing reasonable TTO from vaccine administration, due to insufficient information on current or previous contact exposure, correlation of clinical features with markers of presence of actual virus or viraemia to a herpes case and in the backdrop of localised lesions (with no significant trend in increase frequency and severity) with rapid recovery, a causal role of the vaccine cannot be comprehensively confirmed from assessment of the safety database. The O/E analyses indicated that the number of observed cases for both herpes zoster and oral herpes were significantly less than expected cases. The review of relevant articles available in current literature did not identify any publications describing a causal association between viral herpes infection and COVID-19 VACCINE and no conclusive mechanism of action leading to viral herpes infection after COVID-19 VACCINE ASTRAZENECA vaccination has been identified.

Conclusion

This cumulative review of viral herpes infection with COVID-19 VACCINE ASTRAZENECA vaccination did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern. It is AstraZeneca's opinion that no update to the CDS or RMP is needed. Viral herpes infection will continue to be monitored as part of AstraZeneca's routine surveillance process.

15.2.23 Vulval ulceration

Request:

AstraZeneca received the following requests from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

"The MAH is requested to:

- *Provide a cumulative review of all cases of vulval ulceration from all sources (clinical, post-marketing, and literature). The search strategy should include all relevant PTs related to vulval ulceration (eg,. PTs vulval ulceration, vaginal ulceration, vulvovaginal ulceration etc.) to present cases following Vaxzevria.*
- *Provide an analysis of medically and non-medically confirmed cases, serious and non-serious, providing in a tabular format all the relevant information to assess causality (TTO, concomitant treatment, medical history, outcome, duration of events, etc).*
- *A special emphasis should be put on the identification and analysis of cases with positive re-challenge. Regarding non-medically confirmed cases, these should be assessed as well by the MAH and a summary of the main information should be provided.*
- *Provide a literature review as well as a further discussion on the mechanisms which could lead to vulval ulceration.*
- *Provide an observed vs expected (O/E) analysis (with sensitivity analysis) for all cases of vulval ulceration with a risk window of 0 to 14 days and also including events with unknown TTO. For the calculations of the O/E analysis, the relevant and justifiable background incidence rate should be used.*

AstraZeneca's response to these requests is provided below.

Review of Cases

A cumulative search of the AstraZeneca Global Patient Safety Database through 28 December 2021 was performed for all cases, from all sources coding to any of the following MedDRA PTs: Vulval ulceration, Vaginal mucosal blistering, Vaginal scarring, Vaginal ulceration, Vulvar erosion, Vulvovaginal ulceration, or Genital ulceration.

The search identified a total of 55 cases (39 medically unconfirmed, 16 medically confirmed) indicative of vulvar ulceration, all from spontaneous sources with the majority (54/55) received from Regulatory authorities. Vaccinees were all adult females and where reported age ranged from 18-60 years (49/55) with a median of 27 years of age: 18-24 (16/55), 25-34 (18/55) and 46-60 (3/55). Out of the 55 cases, 6 did not report age. Most of the cases were from the UK (29/55), followed by Spain (8/55), Australia (5/55), Norway (4/55), 2 each from Finland, France, Ireland and 1 each from [redacted].

Overall, these 55 cases reported 55 events (31 reported as nonserious, 24 reported as serious) of interest. The count of adverse events by MedDRA PTs were as follows: Vulval ulceration (21/55), Genital ulceration (18/55), Vaginal ulceration (12/55) and Vulvovaginal ulceration (4/55). Of the 55 cases, TTO was unknown in 10 cases. In the remaining 45 cases, relative to the most recent dose, TTO ranged from 1-15 days, the majority occurring between 1-4 days: 9 events occurred in 1 day, 24 in 2 days, 8 in 3 days, 3 in 4 days and 1 in 15 days. Most cases (53/55) reported only one dose but where only one dose was reported it was not specified if first or second dose.

Two cases reported more than one dose of vaccine. Once case (PPD) reported 2 doses of COVID-19 VACCINE ASTRAZENECA but events reported only pertained to Dose 1: vulval ulceration 4 days after vaccination preceded by headache, pyrexia and myalgia. The second case PPD , a heterologous vaccine dosing. COVID-19 VACCINE ASTRAZENECA (Dose 1) followed by a dose of PFIZER COVID-19 (Dose 2) 4 weeks apart; adverse events of genital ulceration and aphthous ulcer (mouth) occurred 3 days after each vaccine.

Outcomes (53/55) were reported in most cases, and more than half (35/53) had either reportedly resolved with sequelae (1), resolved (22/55) or were resolving (12/55) at the time of reporting. Of the 23 events that had resolved or resolved with sequelae, 13 reported a duration. These ranged from 4-60 days: with a median of 11 days: 4-9 days (10), 10-15 days (3) and 1 case each for 18 days, 30 days and 60 days.

Medically confirmed cases

Table 89 provides a tabulation of the 16 medically confirmed cases (7 serious, 9 nonserious) indicative of vulval ulceration. Six cases provided medical histories of which 4 reported a history considered a confounding factor for vulval ulceration such as infectious mononucleosis, herpes simplex, immunodeficiency and vulval ulceration. In 8 cases the patient had a flu-like illness or other symptoms such as headache, fever, myalgia, malaise between vaccination and vulval ulceration or these were reported on the same day as vulval ulceration. In 3 cases the patient had mouth ulceration or swelling in addition to the vulval ulceration.

Table 89 Overview of Medically Confirmed cases indicative of Vulval ulceration (n=16) cumulative to 28 December 2021

Case details Country/ Age (yrs) Case serious Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Serious Spontaneous - RA	*Genital ulceration (S)*; Mouth swelling; Vaccination site mass; Oropharyngeal pain; Feeling of body temperature change; Headache; Myalgia; Arthralgia	2	Not resolved	Not applicable	None reported	PPD	History of infectious mononucleosis could be a contributory factor.
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; Myalgia; Headache; Pyrexia	1	Resolved	Unk	None reported	None reported	-
PPD /unk Serious Spontaneous - RA	*Vulval ulceration (S)*; Herpes virus infection; Mouth ulceration; Fatigue; Headache; Nausea; Myalgia; Pyrexia; Influenza like illness; Diarrhoea	2	Resolved	Unk	PPD		History of herpes simplex could be a contributory factor.

Table 89 Overview of Medically Confirmed cases indicative of Vulval ulceration (n=16) cumulative to 28 December 2021

Case details Country/ Age (yrs) Case serious Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Non-serious Spontaneous - RA	*Vaginal ulceration (NS)*; Pyrexia; Myalgia	unk	Resolved	9	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*; Vaginal discharge; Malaise	2	Not resolved	Not applicable	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Vaginal ulceration (NS);* Skin discolouration; Pruritus	2	Not resolved	Not applicable	None reported	PPD	History of immunodeficiency could be a contributory factor.
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Oropharyngeal pain; SARS-CoV-2 test negative;	1	Resolving	Not applicable	None reported	None reported	-
PPD Non-serious	*Vulval ulceration (NS)*	2	Not resolved	Not applicable	None reported	None reported	-

Table 89 Overview of Medically Confirmed cases indicative of Vulval ulceration (n=16) cumulative to 28 December 2021

Case details Country/ Age (yrs) Case serious Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
Spontaneous - RA							
PPD Nonserious Spontaneous - RA	*Vulval ulceration (NS)*	2	Not resolved	Not applicable	None reported	None reported	-
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; Pain; Pyrexia	3	Resolved	Unk	None reported	PPD	Labs negative for: Herpes Simplex; PPD ; Mycoplasma Genitalium; Neisseria; History of vulval ulceration could be a contributory factor.
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; Vulvovaginal pain	2	Not resolved	Not applicable	None reported		-
PPD	*Vulval ulceration (S)*;	2	Resolving	Not applicable	None reported	None reported	-

Table 89 Overview of Medically Confirmed cases indicative of Vulval ulceration (n=16) cumulative to 28 December 2021

Case details Country/ Age (yrs) Case serious Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
Serious Spontaneous - RA	Vulvovaginal swelling						
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*	unk	Resolving	Not applicable	None reported	None reported	-
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; Headache; Myalgia; Pyrexia; Vaccination site pain; Fatigue	1	Resolved	60	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*; Genital pain; Abdominal pain; Oropharyngeal pain; Mucosa vesicle; Mouth ulceration; Headache; Pyrexia; Fatigue; Dyspnoea; Petechiae;	2	Resolved with sequelae	9	PPD		Results pending for: Urine Strip Test; Herpes Simplex serology.

Table 89 Overview of Medically Confirmed cases indicative of Vulval ulceration (n=16) cumulative to 28 December 2021

Case details Country/ Age (yrs) Case serious Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
	Cough; Sinusitis						
PPD [redacted] Serious Spontaneous - RA	*Vulval ulceration (S)*; Myalgia; Headache; Pyrexia	4	Resolved	18	None reported	None reported	-

N Number, NS Nonserious, PT Preferred Term, RA Regulatory authority, S Serious, TTO Time To Onset; UK United Kingdom, Unk unknown.

Medically unconfirmed cases

Table 90 provides a tabulation of the 39 medically unconfirmed cases (17 serious, 22 nonserious) indicative of vulval ulceration. Eleven cases provided medical histories of which 5 reported a history considered a confounding factor for vulval ulceration such as vaginal ulceration, immunodeficiency, COVID-19 infection, herpes simplex and genital ulceration. In 1 additional case a concurrent syphilis was a confounding factor (unclear if syphilis was confirmed). In 13 cases the patient had a flu-like illness or other symptoms such as headache, fever, myalgia, malaise between vaccination and vulval ulceration or these were reported on the same day as vulval ulceration. In 4 cases the patient had mouth ulceration in addition to the vulval ulceration.

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Serious Spontaneous	*Genital ulceration (S)*; Back pain	2	unk	Not applicable	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*	2	Resolving	Not applicable	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*	2	Resolving	Not applicable	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Vaginal ulceration (NS)*; Genital rash; Pyrexia; Nausea; Headache	3	Not resolved	Not applicable	None reported	PPD	-
PPD UK/unk Serious Spontaneous - RA	*Genital ulceration (S)*; Chills; Pyrexia; Myalgia;	4	Not resolved	Not applicable	PPD	None reported	-

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
	Injection site urticaria; Headache						
PPD Serious Spontaneous - RA	*Vaginal ulceration (S)*; Pyrexia	2	Not resolved	Not applicable	PPD		-
PPD Non-serious Spontaneous - RA	*Vaginal ulceration (NS)*; Fatigue; Arthralgia; Headache; Pyrexia; Malaise; Chills; Myalgia	2	Not resolved	Not applicable			History of vaginal ulceration could be a contributory factor.
PPD Serious Spontaneous - RA	*Vulvovaginal ulceration (S)*; Back pain	1	Resolving	Not applicable	None reported	None reported	-
PPD Serious Spontaneous - RA	*Genital ulceration (S)*; Achlorhydria; Polymenorrhoea; Genital ulcer syndrome; Hordeolum; Chills; Fatigue; Pruritus; Pyrexia; Pain	2	Resolving	Not applicable	PPD		History of immunodeficiency could be a contributory factor.

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Non-serious Spontaneous - RA	*Vulvovaginal ulceration (NS)*; Genital haemorrhage; Genital infection	1	Resolved	unk	None reported	None reported	-
PPD Serious Spontaneous - RA	*Genital ulceration (S)*; Mouth ulceration;	2	Not resolved	Not applicable	PPD		2 week history of mouth and genital ulcers on vulva during COVID-19 infection (dates were not provided).
PPD Serious Spontaneous - RA	*Vaginal ulceration (S)*; Headache; Pyrexia	2	Resolving	Not applicable	None reported	None reported	swabs confirmed ulcers were non STIs. Sexual health screening negative according to patient.
PPD Serious Spontaneous - RA	*Vulvovaginal ulceration (S)*; Pain in extremity	1	Resolved	9	None reported	None reported	-
PPD	*Vulval ulceration (NS)*;	3	Resolved	15	PPD	None reported	-

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Non-serious Spontaneous - RA	Intermenstrual bleeding						
PPD /unk Serious Spontaneous - RA	*Genital ulceration (S)*; Oral herpes; Ulcer; Pain in extremity; Pyrexia; Fatigue; Headache; Injection site pain; Hyperhidrosis; Chills	1	Not resolved	Not applicable	None reported	PPD	
PPD /unk Serious Spontaneous - RA	*Vaginal ulceration (S)*; Hypopnoea	1	Not resolved	Not applicable	None reported	None reported	-
PPD Serious Spontaneous - RA	*Vaginal ulceration (S)*; Genital herpes;	3	Resolved	11	None reported	PPD	sexual health screening: negative for herpes.
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; PPD; Pyrexia; Headache;	2	Not resolved	Not applicable	PPD	None reported	-

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
	Myalgia; Arthralgia						
PPD Serious Spontaneous - RA	*Vaginal ulceration (S)*	15	Not resolved	Not applicable	PPD	None reported	-
PPD /unk Non-serious Spontaneous - RA	*Genital ulceration (NS)*	2	Not resolved	Not applicable	None reported	PPD	History of herpes simplex could be a contributory factor, although dates were not provided.
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*; Mouth ulceration; Syphilis;	unk	Resolved	unk	PPD	None reported	PPD (if confirmed) could be a contributory factor.
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*; PPD ; Pruritus	4	Resolved	12		PPD	-
PPD	*Vulvovaginal ulceration (NS)*	3	Resolving	Not applicable		None reported	-

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
Non-serious Spontaneous - RA							
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*	2	Resolved	8	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Lymphadenopathy	2	Resolving	Not applicable	None reported	None reported	
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*;	unk	Not resolved	Not applicable	None reported	None reported	-
PPD Serious Spontaneous - RA	*Genital ulceration (S)*; Salivary hypersecretion;	1	Resolved	4	PPD		Swab negative for HSV though patient on PPD. History of genital ulceration could be a

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
							contributory factor.
PPD Serious Spontaneous - RA	*Vaginal ulceration (S)*; Ulcer;	unk	Resolved	Not applicable	PPD	None reported	-
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Arthralgia; Diarrhoea; Injection site pain; Myalgia; Pyrexia	unk	Resolved	unk	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*	unk	Resolving	Not applicable	None reported	None reported	-
PPD /unk Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Groin abscess; Ulcer; Burning sensation; Toothache; Nausea; Headache	1	Not resolved	Not applicable	None reported	None reported	-
PPD	*Vaginal ulceration*	unk	Resolved	unk	None reported	None reported	-

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Non-serious Spontaneous - RA	*(NS)*; Vaginal discharge; Vaginal infection						
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*	2	unk	unk	None reported	None reported	Non-sexually acquired genital ulceration.
PPD Non-serious Spontaneous - RA	*Genital ulceration (NS)*	unk	Resolving	Not applicable	None reported	PPD	-
PPD Serious Spontaneous - RA	*Vulval ulceration (S)*; Genital herpes; Candida infection; Pain;	3	Resolved	4	None reported		The concurrent candida and herpes were not confirmed. The patient suspected it was candida or herpes on day 2 after vaccine then it was an ulcer by day 3

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
PPD Non-serious Spontaneous - RA	*Vaginal ulceration (NS)*; Headache; Chills	3	Resolved	unk	None reported	None reported	-
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Aphthous ulcer; Pain; Flushing; Feeling cold; Nausea	2	Resolved	11	None reported	None reported	Reported as Vulvar aphthous ulcer.
PPD Non-serious Spontaneous - RA	*Vulval ulceration (NS)*; Influenza like illness	2	Resolved	5	None reported	None reported	
PPD Serious Spontaneous - RA	*Genital ulceration (S)*; Genital pain; Mucosal ulceration; Aphthous ulcer (mouth); Pain	3	Resolved	30	None reported	None reported	The patient received AZ vaccine (first dose PPD and Pfizer vaccine(second dose PPD). Three days after each vaccine PPD and

Table 90 Overview of Medically Unconfirmed cases indicative of Vulval ulceration (n=39) cumulative to 28 Dec 2021

Case details Country/Age (yrs) Case seriousness Source	Adverse events (MedDRA PT) Seriousness (*S/NS*)	TTO (days) from 1st dose	Outcome (event of interest)	Duration of events (days)	Concomitant medication	Medical history	Comments
							PPD the patient experienced both genital ulcer and mouth ulcer.

N Number, NS Nonserious, PT Preferred Term, RA Regulatory authority, S Serious, TTO Time To Onset; UK United Kingdom, Unk unknown.

Potential Cases of Rechallenge

Amongst the 55 cases reported, only 2 cases (PPD) reported 2 doses of vaccine, one case PPD only reported events occurring after the 1st dose while the other case reported a heterologous administration of COVID-19 VACCINE ASTRAZENECA and PFIZER COVID-19 vaccine 4 weeks apart, experiencing genital ulceration and aphthous ulcer of the mouth 3 days after each administration. Review of both cases did not provide any information to assess a potential rechallenge though it is noteworthy that the same events occurred with the PFIZER COVID-19 and ASTRAZENECA COVID-19 VACCINE ASTRAZENECA vaccines in the same patient.

Observed versus. Expected Analysis

With regards to Vulvar Ulceration determining an appropriate incidence rate is not possible since causes of this disorder are confounded with other diseases, in this case cancer. AstraZeneca was unable to identify a reliable incidence rate and as such cannot be performed until a reliable incidence rate is identified.

Literature

A cumulative search of Embase, PubMED and InsightMeme was conducted for literature articles on any of: Vulval ulceration, Vaginal mucosal blistering, Vaginal scarring, Vaginal ulceration, Vulvar erosion, Vulvovaginal ulceration, or Genital ulceration following the use of VAXZEVRIA. Except for the one article by González-Romero et al 2021 on *Lipschütz Ulcers*

After the AstraZeneca COVID-19 Vaccine already referenced in the Assessment Report of the 1st PSUR, no additional articles were identified from this literature search.

Potential mechanism

In previously healthy subjects, vulvar ulcers are mostly caused by sexually transmitted microorganisms. Lipschütz's acute vulvar ulceration, is a non-sexually acquired condition characterized by sudden onset of a few painful vulvar ulcer, that is usually preceded by influenza or mononucleosis-like symptoms, such as malaise, fever, asthenia, myalgia, pharyngotonsilitis, lymphadenopathy, and headache. The exact incidence of Lipschütz ulcer is unknown, and the etiology remains unclear, although infectious or idiopathic causes seem to be associated (Pereira et al 2021). One systematic review of 158 cases concluded that Lipschütz's ulceration mainly affects both sexually inactive and, less frequently, sexually active subjects ≤ 20 years of age, presents with ≤ 3 vulvar ulcers, resolves without recurrences within 3 weeks and is temporarily associated with an infection, most frequently a flu-like illness or an infectious mononucleosis syndrome (Vismara et al 2020). In the COVID-19 pandemic era there have been case reports of vulvar aphthous ulcer secondary to COVID-19 infection (Falkenhain-López D 2020, Christl J et al 2021).

Lipschutz ulcer is a diagnosis of exclusion. There is no clear consensus in the literature regarding the precise diagnosis of this pathology. Another systematic review (Sadoghi et al 2019) formulated a diagnostic and therapeutic algorithm defined by two major and four minor criteria. Its onset is associated with an exacerbated immune response to viral diseases, such as Epstein-Barr virus, cytomegalovirus, influenza virus, paratyphoid fever, toxoplasmosis, *mycoplasma pneumoniae*, and mumps. However, in most cases, the association with an infection could not be confirmed. The exact mechanism involved in the formation of ulcers distant to the primary infection site is poorly understood. The suggested theory is of a hypersensitivity reaction to a viral or bacterial infection, leading to deposition of immune complexes in the dermal vessels, which subsequently activates the complement system, resulting in microthrombi formation and consequent tissue necrosis. The differential diagnoses are extensive and include inflammatory processes, drug reactions, trauma, and malignant tumors. Histologic examination is not of diagnostic value because findings are nonspecific (Pereira et al 2021).

Summary

The review of the reported cases noted that most cases lacked sufficient information to exclude other possible aetiologies. It is unclear if the patients who reported this event post first dose of the vaccine received a second dose. There are no cases of positive rechallenge with COVID-19 VACCINE ASTRAZENECA. Only one patient reported two doses of the COVID-19 VACCINE ASTRAZENECA ,but the event occurred after the first dose. A second patient reported the event after COVID-19 VACCINE ASTRAZENECA first dose and Pfizer

vaccine second dose but contained limited information for further assessment. Although laboratory data excluded infections in a few cases, there are other aetiologies that were not investigated. The events appeared to be self-limiting where outcome information was provided (recovered or recovering).

Conclusion

This cumulative review of vulval ulceration with COVID-19 VACCINE ASTRAZENECA vaccination did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern. It is AstraZeneca's opinion that no update to the CDS or RMP is needed at this time.

Vulval ulceration will continue to be monitored as part of AstraZeneca's routine surveillance process.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of safety concerns

At the beginning of the reporting period, the COVID-19 VACCINE ASTRAZENECA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 3.0, dated 28 April 2021 included the following important identified risks, important potential risks, and missing information (see Table 91):

Table 91 Summary of safety concerns – AstraZeneca Core Risk Management Plan for COVID-19 VACCINE ASTRAZENECA (Version no. 3.0, dated 28 April 2021

Risk category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks[a]	Immune mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)
Missing information	Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women
	Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency
	Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease
	Use of COVID-19 VACCINE ASTRAZENECA with other vaccines

[a] CVST without thrombocytopenia added as an Important potential risk

COVID-19 Coronavirus Disease 2019; RMP Risk Management Plan; VAED Vaccine-associated enhanced disease

16.2 Signal evaluation

Two validated signals were closed during the reporting period (Cerebrovascular venous sinus thrombosis[CVST] without thrombocytopenia and Guillain Barré Syndrome[GBS]). A summary of the signal evaluation is provided below.

16.2.1 Closed and rejected/refuted signals

There were no closed and rejected/refuted signals during the reporting period.

16.2.2 Closed signals categorised as important potential risks

There was 1 closed signal, (Cerebrovascular Venous sinus thrombosis, (CVST) without thrombocytopenia), that was categorized as an Important potential risk during the reporting period.

Table 92 Cerebrovascular Venous sinus thrombosis, (CVST) without thrombocytopenia

Characterisation	Summary
Source of the signal	Regulatory Authority
Date detected	02 September 2021
Date closed	02 November 2021
Reference document(s)	August-September 2021 COVID-19 VACCINE ASTRAZENEA Safety Summary Report (Review period: 01 August 2021 – 30 September 2021). October-November 2021 COVID-19 VACCINE ASTRAZENECA Safety Summary Report (Review period: 01 October 2021 – 30 November 2021).
Regulatory procedure reference document(s)	EMEA/H/C/005675/IB/0056
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature of CVST without thrombocytopenia [MedDRA HLT: “Cerebrovascular venous and sinus thrombosis” excluding cases with events from HLT: “Thrombocyopenias” or SMQ: “Hematopoietic thrombocytopenia (narrow)”] with medical review. External Quantitative Signal Detection System, Literature review, Qualitative data (Individual Case Safety Report or Case Series), Clinical data
Outcome of the evaluation	As of 30 September 2021, a total of 458 cases of CVST without thrombocytopenia were identified in the AstraZeneca global safety database. Information on normal platelet count were available in 113 of the 458

Table 92 Cerebrovascular Venous sinus thrombosis, (CVST) without thrombocytopenia

Characterisation	Summary
	cases. In the 18 – 49 age group, 78% occurred in females. Thirty-six (36) fatal cases were identified of which 22 (61%) occurred in vaccinees 18 – 49 years. Time to onset of CVST was within 28 days in 77% of the 334 cases where TTO was reported. Contraceptive use was the most common confounding factor. Reports in the literature were identified describing CVST without thrombocytopenia, gaps in information regarding key factors to allow a better understanding of the reports. The results of the O/E analyses with all CVST without thrombocytopenia (with known normal and unknown platelet counts) suggest that observed cases are more than would be expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is suggestively higher in females than in males. However, the O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases was lower than expected when all cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, the amount of missing information prohibited a meaningful medical assessment of these cases.
Conclusions	Based on a review of currently available information, AstraZeneca considered that a reasonable possibility of a causal relationship between COVID-19 VACCINE ASTRAZENECA and CVST without thrombocytopenia cannot be established at this time. However, CDS Section 4.4 was updated to advise that cases of CVST without thrombocytopenia have been observed although a causal relationship has not been established. In addition, CVST without thrombocytopenia may require different treatment approaches than thrombosis with thrombocytopenia syndrome (TTS) and applicable guidance should be consulted. These updates were internally approved on 02 November 2021.

Table 92 Cerebrovascular Venous sinus thrombosis, (CVST) without thrombocytopenia

Characterisation	Summary
	"Cerebrovascular venous sinus thrombosis without thrombocytopenia" was added as an Important potential risks to the Core Risk Management Plan on 09 December 2021. CVST without thrombocytopenia is kept under close surveillance by AstraZeneca.

CDS Core Data Sheet, CVST Cerebral Venous Sinus Thrombosis, HLT High level Term, MedDRA Medical Dictionary for Regulatory Activities, O/E Observed versus Expected, SMQ Standardised MedDRA Query, TTO Time To Onset, TTS thrombocytopenia syndrome.

16.2.3 Closed signals categorised as important identified risks

There were no closed signals categorised as important identified risks during the reporting period.

16.2.4 Closed signals that are potential risks not categorised as important

There was 1 closed signal Guillain-Barré Syndrome (GBS) considered a potential risk not categorised as important during the reporting period.

Table 93 Guillain-Barré Syndrome (GBS)

Characterisation	Summary
Source of the signal	External quantitative signal detection system
Date detected	31 March 2021
Date closed	29 June 2021
Reference document(s)	July 2021 COVID-19 VACCINE ASTRAZENECA Summary Safety Report (Review period: 01 July 2021 – 30 July 2021) August-September 2021 COVID-19 VACCINE ASTRAZENEA Safety Summary Report (Review period: 01 August 2021 – 30 September 2021).
Regulatory procedure reference document(s)	EMEA/H/C/005675/IB/0034 and EMEA/H/C/005675/IB/0044
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature of GBS [MedDRA SMQ: "Guillain-Barré Syndrome (narrow)"] with COVID-19 VACCINE

Table 93 Guillain-Barré Syndrome (GBS)

Characterisation	Summary
	ASTRAZENECA with medical review according to Brighton collaboration and causality assessment based on WHO-UMC criteria.
Outcome of the evaluation	As of 28 June 2021, a total of 244 cases of GBS were identified in the AstraZeneca global safety database. Using Brighton collaboration criteria (Law B 2021 [A]), 16 of the cases fulfilled Level 1 criteria, 38 fulfilled Level 2 criteria, 42 fulfilled level 3 criteria, 142 fulfilled level 4 criteria, and 6 fulfilled level 5 criteria. Of the 96 cases fulfilling Brighton Collaboration Levels 1, 2 or 3, 10 were assessed as Probable, 21 were assessed as Possible, 18 were assessed as Unlikely, 30 were assessed as Conditional/Unclassified, and 17 were assessed as Unassessable/Unclassifiable. The observed versus expected analysis for all reported cases of GBS with TTO within 14 days, 30 days and 42 days from vaccination suggested that observed cases occurred more frequently than expected. However, an observed versus expected analysis of cases meeting the Brighton Criteria for Level 1, 2 or 3 showed that the observed number of GBS cases were less than the number of expected cases with TTO within 42 days. For cases with TTO within 30 days, the observed number of cases were slightly less than expected. For cases with TTO within 14 days, the observed number of cases were more than expected. The review of the literature did not identify any definitive evidence of a causal association of GBS resulting from COVID-19 VACCINE ASTRAZENECA.
Conclusions	Based on a review of the available information in June 2021, it is AstraZeneca's opinion that a reasonable possibility of a causal relationship between COVID-19 VACCINE ASTRAZENECA and GBS has not been established. No updates to the CDS or RMP were required. As a result of an imposition, GBS was added as an Important identified risks to the EU RMP, approved 02 December 2021. Furthermore, an imposition was

Table 93 Guillain-Barré Syndrome (GBS)

Characterisation	Summary
	received to include a Warning regarding GBS in Section 4.4 (Special warnings and special precautions for use) of the EU SmPC. It should be noted that during the late-breaking period of this PSUR, AstraZeneca validated the signal for GBS. AstraZeneca is further reviewing this topic as part of internal signal evaluation processes and will provide an update in the next PSUR. See Section 14 for additional information.

CDS Core Data Sheet, EU European Union, GBS Gullain-Barre Syndrome, HLT High level Term, MedDRA Medical Dictionary for Regulatory Activities, O/E Observed versus Expected, TTO Time To Onset, RMP Risk Management Plan, TTS thrombocytopenia syndrome, SMQ Standardised MedDRA Query,.

16.2.5 Closed signals that are identified risks not categorised as important

There were no closed signals that are identified risks not categorised as important during the reporting period.

16.3 Evaluation of risks and new information

This section presents data from the AstraZeneca global safety database obtained using search strategies inclusive of all available data in the database. Numbers presented here may differ from those presented in the Appendix 2 summary tabulations (also from the AstraZeneca global safety database), where the search strategies are specific to the requirements for the summary tabulations.

Period data may include case reports which have been received prior to this period but where follow-up information have been obtained during the reporting period. Seriousness has been evaluated and presented at the AE level, which may differ from seriousness at the report level. Furthermore, for the Regulatory Authority reports received in the UK, in the absence of medical confirmation, the seriousness assessment provided by the initial reporter is used as the source data. Thus, there are nearly double the number of non-medically confirmed, serious adverse events than non-medically confirmed cases included in these analyses and may indicate a different understanding of seriousness definitions for those events reported by non-medically trained individuals. Lastly, cases removed from the analysis due to identified data quality issues will be noted in the appropriate sections of the tables and analysis.

16.3.1 New information on important potential risks

All Important potential risks included in Section 16.1 and included in Table 94 below are kept under close surveillance by AstraZeneca.

Table 94 Important potential risks presented in Core RMP (Version 3.0; dated 28 April 2021

Section/Topic	Core RMP
Important potential risk	Immune-mediated neurological conditions Vaccine-associated enhanced disease Cerebral venous sinus thrombosis (CVST) without thrombocytopenia[a]

[a] Risk of CVST without thrombocytopenia added as in Important potential risk to the Core RMP with v 5.0; dated 09 December 2021

RMP Risk Management Plan

16.3.1.1 New information on Immune-mediated neurological conditions / Nervous system disorders, including immune-mediated neurological conditions during the reporting period

During the period covered by this report (29 June 2021 – 28 December 2021), a total of 11529 processed cases from literature, clinical studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 11529 cases, 2507 were medically confirmed (serious 1221, non-serious 1286) and 9022 were non-medically confirmed (serious 3898, non-serious 5124). The most commonly reported PTs were Paraesthesia (6390), Hypoaesthesia (3655), Neuralgia (894), Guillain-Barre syndrome (848), Sensory disturbance (582), Neuropathy peripheral (242), Sensory loss (143), Myelitis transverse (95), Polyneuropathy (95), Optic neuritis (90), Encephalitis (83), Multiple sclerosis (65), Myelitis (62), Multiple sclerosis relapse (61), Neuritis (48), Demyelination (41), Acute disseminated encephalomyelitis (35), Chronic inflammatory demyelinating polyradiculoneuropathy (33), Peripheral sensory neuropathy (27), Miller Fisher syndrome (22).

Cumulatively through 28 December 2021, 31278 cases from literature, clinical studies, non-interventional studies and spontaneous sources have reported 36198 PTs within the concept of Immune-mediated neurological disorders. The most commonly reported PTs are Paraesthesia (18105), Hypoaesthesia (10927), Neuralgia (2375), Guillain-Barre syndrome (1340), Sensory disturbance (889), Neuropathy peripheral (481), Sensory loss (412), Myelitis transverse (173), Optic neuritis (152), Encephalitis (140), Multiple sclerosis (135), Polyneuropathy (132), Multiple sclerosis relapse (118), Myelitis (93), Demyelination (80), Neuritis (70), Acute disseminated encephalomyelitis (54), Miller Fisher syndrome (48), Peripheral sensory neuropathy (43).

Literature

Multiple Sclerosis

Patients with MS are at increased risk for acquiring infections and disease-modifying therapies (DMTs), which suppress or modulate the immune system, have been associated with increased risk of infections. For this reason, vaccination as the most efficient measure to prevent infections is imperative in this population. Yamout et al 2021 determined that COVID-19 vaccines are safe to use in patients with MS treated with DMTs.

AstraZeneca Comment: While the AstraZeneca vaccine has recently been associated thrombotic events, mostly venous sinus thrombosis, and mainly females, these events are rare and the benefits of the vaccine still outweigh the risks.

Polyradiculoneuropathy

Loo et al 2022 reviewed records of all persons presenting with acute-onset polyradiculoneuropathy from 01 January 2021 to 30 June 2021 who were admitted to two neuroscience centers in the United Kingdom. Of 24 persons with acute-onset polyradiculoneuropathy, 14 had received the AstraZeneca vaccine. Among the AstraZeneca vaccine recipients, facial weakness in 9 persons, bulbar weakness in 7, and the bifacial weakness and distal paresthesias GBS variant in 3, were more common than in historical controls (P=.01; P=.004, and P=.002, respectively).

AstraZeneca Comment: A 2.6-fold (95% confidence interval: 1.98-3.51) increase in admissions for acute-onset polyradiculoneuropathy was noted during the studied time frame compared to the same period in the previous 3 years. Despite a low risk, smaller than that of SARS-CoV2 infection and its complications, exposure to the first dose of the AstraZeneca vaccine may be a risk factor for acute-onset polyradiculoneuropathy, characterized by more common cranial nerve involvement.

Conclusion

During the review period, AstraZeneca evaluated, but did not validate a signal for GBS with COVID-19 VACCINE ASTRAZENECA (See Section 16.2.4). However, during the Late-breaking period, a signal for GBS was validated and is being further reviewed as part of internal signal evaluation processes (Section 14) There have been no additional signals or information regarding Immune mediated neurological disorders with COVID-19 VACCINE ASTRAZENECA received during the reporting period.

Immune-mediated neurological conditions with COVID-19 VACCINE ASTRAZENECA will continue to be kept under close surveillance by AstraZeneca.

More detailed information regarding this important potential risk is provided in Section 16.4.2.

Reviews of specific topics relating to Immune-neurological conditions with COVID-19 VACCINE ASTRAZENEC, including Acute Disseminated Encephalomyelitis, Encephalitis (including fatal), and Transverse myelitis, as requested by Health Authorities for inclusion in this PSUR are included in Section 16.3.1.1.1, Section 16.3.1.1.2 and Section 16.3.1.1.3, respectively.

16.3.1.1.1 Acute Disseminated Encephalomyelitis (ADEM)

Request

AstraZeneca received the following request from PRAC in the AR for the 1st COVID-19 VACCINE ASTRAZENECA PSUR (review period: 29 December 2021 – 28 June 2021):

"ADEM should continue to be closely monitored and discussed in the next PSUR, including an updated O/E analysis and a discussion of cases from the literature."

AstraZeneca's response to this request is below.

Review of Cases

Interval Review (29 June 2021 – 28 December 2021)

A search of the AstraZeneca global safety database was conducted for interval adverse event data (from 29 June 2021 to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PT: Acute disseminated encephalomyelitis' in association with the use of COVID-19 VACCINE ASTRAZENECA.

The search identified 35 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. 34 cases were spontaneously reported and 1 was a literature report, no cases were from other sources such as solicited or clinical.

Of the 35 cases, 35 (100.0%) cases were serious and 16 (45.7%) cases were reported by healthcare professionals (medically confirmed). 4 cases had a fatal outcome.

Of the 35 reports: 9 (25.7%) were from the UK, 8 (22.9%) were from Germany; 5 (14.3%) cases were from Australia; 2 (5.7%) each were from Brazil, Greece and Italy; 1 (2.9%) each were from [redacted]

There were 18 (51.4%) case reports for female vaccinees and 17 (48.6%) were for male vaccinees. The age range was 23-90 years of age: 23 (65.7%) vaccinees were between age group of 18≤65 years of age; 10 (28.6%) vaccinees were >65 years of age; for 2 (5.7%) the vaccinees the age was unknown.

The Brighton collaboration (Law B 2021 [B]) criteria (BCC) were used for the review of the data available in the case reports. Based on this approach, out of the 35 cases: No cases fulfilled level 1 criteria; 3 cases fulfilled level 2 criteria; 4 cases fulfilled level 3 criteria; 17 cases fulfilled level 4 criteria;11 cases fulfilled level 5 criteria. In addition to the BCC, the published Brighton Case Definition for GBS (Law B 2021 [A]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, malignancy, infections, use of vaccines, surgery).

Brighton Collaboration criteria Level 1

None out of 35 case reports fulfilled Brighton collaboration level 1 criteria according to classification by clinical course, examination features and/or level of certainty.

Brighton Collaboration criteria Level 2

Three (3) out of 35 case reports fulfilled Brighton collaboration level 2 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory and are presented in Table 95 below. One report was reported in a female vaccinee and two were reported in males and the age range was 53-71 years. There were no known relevant risk factors or confounding factors. The time to onset were between 0 to 49 days in these cases. The median time to onset was 7 days. One of the three cases had a fatal outcome. 1 case was reported to occur after the 2nd dose and the dose information was unknown in the remaining 2 cases. Out of the 3 cases fulfilling the BCC 2 criteria, 2 cases were assessed as possible, and 1 case was assessed as unlikely per the WHO-UMC Causality assessment criteria Out of the 2 cases that were assessed as possible 1 had other confounding factors or alternate etiologies such as flu vaccine, neoplasm in lung with possible metastasis to the brain. 1 case had limited information in regards to medical history, comorbidities, concomitant medications, and investigations.

Table 95 Cases of ADEM Fulfilling Brighton Collaboration criteria Level 2 (N=3)

Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Outcome	WHO-UMC Causality Assessment	Additional Comment
PPD / YES	PPD	PPD	Unknown /7 days	Not recovered	Possible	The timing of AZ vaccine exposure in relation to onset of symptoms and diagnosis was contradictive in the narrative. Onset about 14 to 15 days after flu vaccine, as likely etiology. AZ vaccine was several weeks prior with only normal reactogenicity post AZ vaccine. Exam reportedly showed possible evidence of PPD , however pathology not available or not yet done.
PPD / YES	PPD	Unknown	2nd dose/ 0 days	Not Recovered	Possible	No other work up other than MRI noted: no information on past or present infections, pre-existing conditions, diagnoses, other medications, other pertinent brain findings. Changes after first dose and different changes after second dose of vaccine, possibly.

Table 95 Cases of ADEM Fulfilling Brighton Collaboration criteria Level 2 (N=3)

Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Outcome	WHO-UMC Causality Assessment	Additional Comment
PPD / YES	PPD	Unknown	Unknown/ 49 days	Died	Unlikely	49 Day TTO. Narrative suggests patient died and the cause of death was ADEM. However, the event occurred outside the risk window (49 days) and the death occurred after noted improvement in the patient's lesions. The date of death was unknown. PPD was noted as a possible etiology. Pending follow up for autopsy results.

AZ AstraZeneca, F Female,M Male, MRI Magnetic Resonance Imaging, TTO Time To Onset, UMC Uppsala Monitoring Centre, WHO World Health Organization.

Brighton Collaboration Level 3

Four (4) out of 35 case reports fulfilled Brighton collaboration level 3 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory testing and are presented in Table 96. Two (2) reports were reported in females and 2 were reported in males and the age range was 61 - 63 years. 3 cases did not report any relevant risk factors or confounding factors. Risk factors/confounding factors in 1 of the 4 cases included hypothyroidism, hypertension and Plasmapheresis. Time to onset ranged between 2 to 43 days. Median time to onset was 22 days. The outcome in 2 cases was recovered with sequelae, not recovered in 1 case and unknown in 1 case. Out of the 4 cases fulfilling BC 3 criteria, 3 cases were assessed as possible, as these occurred within the risk window of 42 days and 1 case was assessed as unlikely, as these occurred outside the risk window of 42 days per WHO-UMC Causality assessment criteria. All the 3 cases that were assessed as possible had limited information in regards to medical history, comorbidities, concomitant medications, and investigations.

Table 96 Cases of ADEM Fulfilling Brighton Collaboration criteria Level 3 (N=4)

Case ID/ Country/ Serious (Y/N)	Age (Years) / Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Outcome	WHO-UMC Causality Assessment	Additional Comment
PPD / YES	PPD	PPD	1st Dose/2 days	Not recovered	Possible	No supportive workup information, h/o past or present infections, concomitant medications and other pertinent brain findings provided. Patient has a history of hypothyroidism, hypertension and plasmapheresis; it is not known what the underlying disorder treated with plasmapheresis is.

Table 96 Cases of ADEM Fulfilling Brighton Collaboration criteria Level 3 (N=4)

Case ID/ Country/ Serious (Y/N)	Age (Years) / Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Outcome	WHO-UMC Causality Assessment	Additional Comment
PPD / YES	PPD	Unknown	1st dose/ 43 days	Recovered with sequelae	Unlikely	TTO is outside of risk window.
PPD / YES	PPD	Unknown	1st dose/ 8 days	Recovered with sequelae	Possible	Only weakness and convulsion events noted. No work up information.
PPD	Unk/ PPD	PPD	Unknown/ Unknown	Unknown	Possible	Although unknown specific TTO, it falls within the range of expected TTO. BC classification was based PPD PPD WHO UMC – Possible with limited information.

ADEM Acute Disseminated Encephalomyelitis; AZ AstraZeneca, F Female; M Male, MRI Magnetic Resonance Imaging, TTO Time To Onset, UMC Uppsala Monitoring Centre, WHO World Health Organization.

Brighton Collaboration Level 4

17 out of 35 case reports fulfilled Brighton collaboration level 4 criteria. These cases did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the case.

Brighton Collaboration Level 5

11 out of 35 case reports fulfilled Brighton collaboration level 5 criteria, (ie, ADEM (excluded due to an alternative diagnosis).

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of ADEM is presented with different risk windows (14 days, 30 days, and 42 days) in Table 97. This included all reported cases irrespective of the Brighton criteria level. The risk window of 2-42 days was included from the Brighton case definition (Law B 2021 [B]). As a conservative approach cases with time to onset within 2 days were included in the analysis. The number of observed cases were provided both with and without cases with unknown time to onset as a conservative approach.

In order to provide an accurate incidence rate for this rare event, a meta-analysis using random-effect model was done based on data from years 2017-2019 from databases (ES_BIFAP_PC, ES_BIFAP_PCHOSP, ES_FISABIO, ES_SIDIAP_PC, ES_SIDIAP_PCHOSP, IT_ARS, UK_CPRD) presented in the revised ACCESS protocol (Willame et al 2021 [B]).

Table 97 Observed Versus Expected Analysis for all reports of ADEM (Global reports)

Adverse Events	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global) ACCESS Incidence Rate ADEM	14	0.15	291626957	27	16.77	1.61 (1.06 - 2.34)	Observed significantly > expected
	30	0.15	291626957	30	35.93	0.83 (0.56 - 1.19)	Observed < expected
	42	0.15	291626957	31	50.3	0.62 (0.42 - 0.87)	Observed significantly < expected
Overall (Global) ACCESS Incidence Rate including cases with an unknown time to onset	14	0.15	291626957	46	16.77	2.74 (2.01 - 3.66)	Observed significantly > expected
	30	0.15	291626957	49	35.93	1.36 (1.01 - 1.8)	Observed significantly > expected
	42	0.15	291626957	50	50.3	0.99 (0.74 - 1.31)	Observed < expected

Incidence rate (IR) = 0.15/100,000 person years. Source: Willame et al 2021 [B] (Meta-analysis IR from 2017-2019 ADEM-Narrow)

ADEM Acute Disseminated Encephalomyelitis; CI Confidence Interval; E Expected; IR Incidence rate; O Observed

An observed versus expected analysis of cases meeting case definition according to Brighton Criteria for Level 1, 2 or 3, based on clinical course, examination such as brain histopathology, focal/multifocal CNS abnormalities, brain magnetic resonance imaging (MRI) or recurrence or relapse of illness since the symptomatic nadir and no alternative etiology (Law B 2021 [B]) are presented in Table 98.

Table 98 Observed Versus Expected Analysis for cases for ADEM meeting the Brighton Criteria Level 1, 2 or 3 (Global reports)

Adverse Events	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global) ACCESS Incidence Rate ADEM BCC levels 1-3	14	0.15	291626957	7	16.77	0.42 (0.17 - 0.86)	Observed significantly < expected
	30	0.15	291626957	8	35.93	0.22 (0.1 - 0.44)	Observed significantly < expected
	42	0.15	291626957	8	50.3	0.16 (0.07 - 0.31)	Observed significantly < expected
Overall (Global) ACCESS Incidence Rate ADEM BCC levels 1-3 including cases with an unknown time to onset	14	0.15	291626957	11	16.77	0.66 (0.33 - 1.17)	Observed < expected
	30	0.15	291626957	12	35.93	0.33 (0.17 - 0.58)	Observed significantly < expected
	42	0.15	291626957	12	50.3	0.24 (0.12 - 0.42)	Observed significantly < expected

Incidence rate (IR) = 0.15/100,000 person years. Source: Willame et al 2021 [B] (Meta-analysis from revised ACCESS protocol IR from 2017-2019 ADEM-Narrow)

ADEM, Acute Disseminated Encephalomyelitis; CI, Confidence Interval; E, Expected; IR, Incidence rate; O, Observed

Additionally, as per the PRAC request, the observed versus expected analysis is presented with stratification by age for the EEA, UK regions based on the available exposure data, this is presented in Table 99. Incidence rates were calculated based on meta-analysis estimates of revised ACCESS rates using random-effect model with data from the databases (ES_BIFAP_PC, ES_BIFAP_PCHOSP, ES_FISABIO, ES_SIDIAP_PC, ES_SIDIAP_PCHOSP, IT_ARS, UK_CPRD) (Willame et al 2021 [B]). Sensitivity analyses are provided in Appendix 9.

Table 99 Observed Versus Expected Analysis for ADEM cases stratified by age for EEA/UK regions

AEs	Risk window	IR[a] / 100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Age 18-49	14	0.15	27716022	12	1.59	7.55 (3.9 - 13.18)	Observed significantly > expected
	30	0.15	27716022	13	3.41	3.81 (2.03 - 6.52)	Observed significantly > expected
	42	0.15	27716022	13	4.78	2.72 (1.45 - 4.65)	Observed significantly > expected
Age 50-59	14	0.07	19552392	4	0.52	7.69 (2.1 - 19.7)	Observed significantly > expected
	30	0.07	19552392	5	1.12	4.46 (1.45 - 10.42)	Observed significantly > expected
	42	0.07	19552392	5	1.57	3.18 (1.03 - 7.43)	Observed significantly > expected
Age 60-69	14	0.16	28510714	5	1.75	2.86 (0.93 - 6.67)	Observed > expected
	30	0.16	28510714	5	3.75	1.33 (0.43 - 3.11)	Observed > expected
	42	0.16	28510714	5	5.25	0.95 (0.31 - 2.22)	Observed < expected
Age 70-79	14	0.1	14795684	2	0.57	3.51 (0.42 - 12.67)	Observed > expected
	30	0.1	14795684	2	1.22	1.64 (0.2 - 5.92)	Observed > expected
	42	0.1	14795684	3	1.7	1.76 (0.36 - 5.16)	Observed > expected

[a] Source:Willame et al 2021 [B] (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)
[b] Exposure until 28 November 2021 for EEA/UK.

ADEM Acute Disseminated Encephalomyelitis; CI Confidence Interval; E Expected; EEA European Economic Area; IR Incident Ratio; O Observed; PY Patient years; UK United Kingdom.

An observed versus expected analysis of cases meeting case definition according to Brighton Criteria for Level 1, 2 or 3 is presented in Table 100.

Table 100 Observed Versus Expected Analysis for ADEM cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions

Age group	Risk Window	IR[a] / 100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
Age 18-49 (BCC 1-3)	14	0.15	27716022	2	1.59	1.26 (0.15 - 4.54)	Observed > expected
	30	0.15	27716022	2	3.41	0.59 (0.07 - 2.12)	Observed < expected
	42	0.15	27716022	2	4.78	0.42 (0.05 - 1.51)	Observed < expected
Age 50-59 (BCC 1-3)	14	0.07	19552392	1	0.52	1.92 (0.05 - 10.71)	Observed > expected
	30	0.07	19552392	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
	42	0.07	19552392	1	1.57	0.64 (0.02 - 3.55)	Observed < expected
Age 60-69 (BCC 1-3)	14	0.16	28510714	2	1.75	1.14 (0.14 - 4.13)	Observed > expected
	30	0.16	28510714	2	3.75	0.53 (0.06 - 1.93)	Observed < expected
	42	0.16	28510714	2	5.25	0.38 (0.05 - 1.38)	Observed < expected
Age 70-79 (BCC 1-3)	14	0.1	14795684	0	0.57	0 (0 - 6.47)	Observed < expected
	30	0.1	14795684	0	1.22	0 (0 - 3.02)	Observed < expected
	42	0.1	14795684	0	1.7	0 (0 - 2.17)	Observed < expected

[a] Source: Willame et al 2021 [B] (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)
[b] Exposure until 28 November 2021 for EEA/UK.

ADEM Acute Disseminated Encephalomyelitis, BC Brighton Criteria; CI Confidence Interval; E Expected; EEA European Economic Area; IR Incident Ratio; O Observed; PY Patient years; UK United Kingdom.

The observed versus expected analysis of all cases of ADEM suggested that the observed cases of ADEM cases are less and/or significantly less than number of expected cases in the risk windows 30 and 42, while for the risk window 14 the analysis suggest that the observed cases of ADEM are significantly more than the number of expected cases. When unknown cases are added to the observed numbers, observed cases are significantly more than expected for the 30-day risk window. However, an observed versus expected analysis of cases meeting BCC levels 1-3 showed that the observed number ADEM cases fulfilling case definition are less and/or significantly less than number of expected cases in all risk windows.

When observed versus expected analyses are stratified by age in EEA/UK and different risk windows (14, 30, 42), numbers of cases become very small resulting in observed as greater than expected for some age groups. The incidence rates used were a meta-analysis estimates using random-effect model from the different databases from Willame et al 2021 [B]. The observed versus expected analysis for cases meeting the Brighton Criteria for Level 1, 2 or 3 and stratified by age group with different risk windows (14, 30 and 42 days) suggested that observed cases are more than expected for some age groups. Also, there is too much variability in these data to make an assessment.

Further review of cases in these groups where observed were above expected showed that most cases had insufficient information to make any causality assessment. Of the 35 cases reported during the reporting period, only 7 cases met BCC Level 1-3.

Literature

While there were literature reports of ADEM with different vaccines (SARS-CoV-2 mRNA vaccine, Gam-COVID-Vac, Sinovac) (Goss et al 2021 and Bhavsar et al 2016).

Rinaldi et al 2021 describes a case of ADEM presenting 2 weeks after receiving the first dose of ChAdOx1 nCoV-19 vaccine. A PPD-year-old PPD developed numbness in PPD two weeks after receiving the first dose of ChAdOx1 nCoV-19. PPD condition worsened in a few days: numbness extended to the PPD and PPD progressively experienced PPD Symptoms persisted for one week but then spontaneously improved. MRI showed PPD All lesions, except the PPD , were contrast-enhancing. Cerebrospinal fluid revealed PPD with no tumor cells or infectious agent detected at PCR. Serology for infectious/autoimmune diseases and total-body CT resulted negative. Clinical and neuroradiological improvement ensued right after a 5-day course of high-dose PPD .

AstraZeneca Comment: AZ Comment: Based on the limited clinical information provided, the patient was classified as BC Level 2. However, follow-up to confirm ADEM is not

available. Based on the work up provided and the absence of other etiologies, if follow-up confirms the diagnosis of ADEM , this would be a probable case.

In the five case series of demyelinating events in Camera et al 2021 four of which were after the AZ vaccine exposure, 2 of which were facial diplegia and pre-existing relapsing remitting TM and did not show any evidence of ADEM. 2 cases; a PPD year old PPD and PPD year old PPD had clinical picture suggesting ADEM with a time to onset that was within the risk window.

The authors concluded that it was unclear whether the association was greater than chance or whether the Oxford-AstraZeneca vaccine has a greater incidence because used more frequently in the UK than the Pfizer vaccine. However, the authors noted that viral illnesses and vaccinations have been reported to trigger demyelinating events, including MOG-IgG disease, associated with ADEM.

AstraZeneca Comment: One case (PPD year old PPD) was assessed as BC level 2; follow-up information, exclusion criteria for ADEM was not available. The case was assessed as possible due to time to onset with WHO-UMC criteria, however, limited information was available on confounding factors, medical history and concomitant medications. No etiological work-up was provided. The second case (PPD-year-old PPD) was assessed as BC level 2; follow-up information, exclusion criteria for ADEM was not available. The case was assessed as possible due to time to onset with WHO-UMC criteria, however, limited information was available on confounding factors, medical history and concomitant medications. No etiological work-up was provided.

Summary

Of the 35 cases of ADEM reported in the period of this report, most of the cases occurred in the age group between 18 and 65 years with no significant difference between the genders. 16 were medically confirmed and serious, 4 cases had a fatal outcome. None of the 35 cases met the Brighton Collaboration level 1 criteria. 3 cases met the level 2 criteria, out of which 2 were assessed as possible (one with confounding factors and 1 with limited information) and 1 was assessed as unlikely using the WHO-UMC causality assessment criteria. 4 cases were assessed as level 2 of the Brighton Collaboration criteria, of these 3 were assessed as possible with limited information and 1 was assessed as unlikely. The observed versus expected analysis for cases meeting the Brighton Criteria for Level 1, 2 or 3 and stratified by age group with different risk windows (14, 30 and 42 days) suggested that observed cases are more than expected for some age groups. However, there was too much variability in these data to make an assessment. Literature review for this period did not establish a definitive causal association between COVID-19 vaccine and ADEM.

Viral illnesses and vaccinations have been reported to trigger demyelinating events, including MOG-IgG disease, associated with ADEM. Although ADEM is a disease associated with vaccinations, the review of cases of ADEM reported with COVID-19 VACCINE ASTRAZENECA along with the observed vs. expected analysis and literature review did not identify a safety signal.

Conclusions

Based on the currently available information, a causal relationship between ADEM and COVID-19 VACCINE ASTRAZENECA has not been established. No updates to product labelling or RMP are needed.

Surveillance of ADEM will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the AESI of Nervous system disorders, including immune-mediated neurological conditions.

16.3.1.1.2 Encephalitis, including fatal

Request

AstraZeneca received the following request from PRAC in the AR for the 7th SSR (review periods: 01 August 2021 – 30 September 2021):

"Encephalitis should continue to be closely monitored. Moreover, the MAH should provide a discussion of fatal cases including detailed information. The MAH should also discussed cases published in literature."

AstraZeneca's response to this request is provided below.

Review of Cases

Interval period (29 June 2021 – 28 June 2021)

A search of the AstraZeneca global safety database was conducted for interval adverse event data (29 June 2021 to 28 December 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using the narrow MedDRA SMQ: Noninfective Encephalitis (excluding Acute disseminated encephalomyelitis) and HLT: Encephalopathy with COVID-19 VACCINE ASTRAZENECA.

The search identified 165 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 165 cases, 158 cases were spontaneously reported, 6 cases were from Literature, and 1 case was from post-marketing solicited reports.

Of the 165 cases, 162 (98.2%) cases were serious and 3 (1.8%) were non-serious. 69 (41.8%) cases were reported by healthcare professionals (medically confirmed) and 96 (58.2%) cases were not medically confirmed. The Adverse events outcome were as follows: There were 4 (2.4%) cases with fatal outcome, 55 (33.3%) cases were Not recovered, 25 (15.2%) cases were Recovered, 8 (4.8%) cases were Recovered with Sequelae, 40 (24.2%) cases were Recovering and 33 (20%) were reported as Unknown outcome.

Out of the 165 reports, 41 (24.8%) were from the UK, 35 (21.2%) cases were reported from Germany, 16 (9.7%) cases from Australia, 15 (9.1%) cases each from Italy, 10(6.1%) cases were reported from Spain, 8 (4.8%) cases from France, 7 (4.2%) from Brazil, 5 (3.0%) each from India and Poland, 3 (1.8%) cases each from Mexico, 2 (1.2%) from Belgium, 1 (0.6%) cases each from [redacted]

There were 90 (54.5%) reports for female vaccinees, 74 (44.8%) were for male vaccinees and the gender was missing in 1 (0.6%) case. The age range was 18-96 years of age; 120 (72.7%) vaccinees were between age group of 18-<65 years of age (Adult), 38 (23.0%) vaccinees were >65 years of age, 7 (4.2%) vaccinees the age was unknown. Median age was found to be 57 years.

The adverse event preferred terms reported included Encephalitis (83), Encephalopathy (21), Encephalitis autoimmune (20), Noninfective encephalitis (16), Encephalomyelitis (13), Autoimmune encephalopathy (5), Hypoxic-ischemic encephalopathy (4), Posterior reversible encephalopathy syndrome (3), Immune-mediated encephalitis (2), Immune-mediated encephalopathy (2), Limbic encephalitis (2), Encephalitis post immunization (1), Non infective encephalomyelitis (1), Post resuscitation encephalopathy (1), Acute encephalitis with refractory, repetitive partial seizures (1), Acute hemorrhagic leukoencephalitis (1), Hashimoto's encephalopathy (1), Hypertensive encephalopathy (1).

All the cases during the interval period have been reviewed and analyzed using Brighton Collaboration (BC) classification summarized along with cumulative data in below sections.

Cumulative Review through 28 December 2021

A search of the AstraZeneca global safety database for reports of encephalitis with COVID-19 VACCINE ASTRAZENECA was conducted through 28 December 2021 using the same search criteria described above.

The search identified 270 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 270 cases, 262 cases were spontaneously reported, 6 cases were

from Literature, 1 case is from study ICMR/SII-AZD-COVID-19/2020, and 1 case was from post-marketing solicited reports.

Of the 270 cases, 265 (98.1%) cases were serious and 5 (1.9%) were non-serious. 135 (50%) cases were reported by healthcare professionals (medically confirmed) and 135 (50%) cases were not medically confirmed. The Adverse events outcome were as follows: There were 8 (3%) cases with fatal outcome, 84 (31.1%) cases were Not recovered, 47 (17.4%) cases were Recovered, 11 (4.1%) cases were Recovered with Sequelae, 70 (25.9%) cases were Recovering and 50 (18.5%) were reported as Unknown outcome.

Out of the 270 reports, 85 (31.5%) were from the UK, 45 (16.7%) cases were reported from Germany, 22 (8.1%) cases from Italy, 20 (7.4%) cases each from Australia and France, 17 (6.3%) cases were reported from Spain, 9 (3.3%) cases from Brazil, 7 (2.6%) from India, 5 (1.9%) from Belgium and Poland, 4 (1.5%) cases each from Mexico, 3 (1.1%) from Romania, 2 (0.7%) cases each from Argentina, Finland, Greece, Hungary, Netherlands, Slovakia, and Slovenia, and 1 (0.4%) report each from [redacted]

There were 145 (53.7%) reports for female vaccinees, 123 (45.6%) were for male vaccinees and the gender was missing in 2 (0.7%) cases. The age range was 18-96 years of age; 183 (67.8%) vaccinees were between age group of 18-<65 years of age, 70 (25.9%) vaccinees were >65 years of age, 1 (0.4%) for <18 years of age and for 16(5.9%) vaccinees the age was unknown. Median Age was found to be 57 years.

In 21 case reports, the events were reported to have occurred after the second dose of vaccine. The Median TTO for all the cases was found to be 9 days. 139 (51.5%) out of 270 cases were within the risk window of 2-42 days, 40 (14.8%) cases were less than (0-1 days) and/or greater than (> 42 days) risk window and 91 (33.7%) cases have unknown TTO.

The adverse event preferred terms reported included Encephalitis (140), Encephalopathy (36), Encephalitis autoimmune (28), Noninfective encephalitis (21), Encephalomyelitis (18), Hypoxic-ischemic encephalopathy (7), Autoimmune encephalopathy (7), Posterior reversible encephalopathy syndrome (6), Limbic encephalitis (5), Encephalitis post immunization (2), Immune-mediated encephalitis (2), Immune-mediated encephalopathy (2), Non infective encephalomyelitis (2), Post resuscitation encephalopathy (2), Acute encephalitis with refractory, repetitive partial seizures (1), Acute haemorrhagic leukoencephalitis (1), Encephalitis brain stem (1), Hashimoto's encephalopathy (1), Hypertensive encephalopathy (1), Opsoclonus myoclonus (1), Reversible splenial lesion syndrome (1).

The Brighton collaboration (Law B 2021) criteria were used for the review of the data available in the case reports. Based on this approach, out of the 270 cases, 9 fulfilled level 2

criteria, 26 fulfilled level 3 criteria, 140 fulfilled level 4 criteria and 95 cases fulfilled level 5 criteria.

In addition to the Brighton collaboration criteria, the published Brighton Case Definition for Encephalitis (Law B 2021 [C]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors such as HIV, immunosuppression or deficiency, exposure to virus, animal exposure and other vaccines.

Brighton Collaboration Level 1

None out of the 270 case reports fulfilled Brighton collaboration level 1 criteria. To fulfil this classification surgical procedures to obtain tissue samples or pathology/histopathology/autopsy reports are required and be indicative of acute inflammation of CNS parenchyma (Law B 2021 [C]). No case report fulfilled this classification.

Brighton Collaboration Level 2

Nine (9) out of the 270 cases fulfilled Brighton collaboration level 2. The cases fulfil this classification by the clinical course, examination findings and test results indicative of Encephalitis based on clinical evaluation of level on consciousness/lethargy/personality change, response to different stimuli/ability to make eye contact/seizures and indicators of CNS inflammation such as fever, CSF pleocytosis, Electroencephalography (EEG) changes consistent with encephalitis or brain neuroimaging with evidence of acute inflammation or demyelination (Law B 2021 [C]). These cases are summarized in Table 101 below.

Table 101 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment/Causality Assessment
1	PPD / YES	PPD	PPD	7/ #1st Dose	Not recovered	Deep vein thrombosis suggests vascular disease; EEG and CSF show PPD / Limited information to make any causality assessment.
2	PPD / YES	Unknown / PPD	Not provided	Unknown/ #1st Dose	Recovering	CSF and image consistent/ Limited information to make any causality assessment
3	PPD / YES	PPD	PPD	Unknown/ #Unknown	Recovering	Work up positive for MRI showing PPD . Seems to have responded to treatment with PPD / Alternative causal factors noted

Table 101 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment/Causality Assessment
4	PPD / YES	PPD	Not provided	20/ #1st Dose	Ongoing	Possible risk factor: PPD , limited imaging result information, CSF results described as "highly abnormal" but no signs of infection; Limited information to make any causality assessment
5	PPD / YES	PPD	Not reported/Not reported	15/ #1st Dose	Not reported	MRI findings (PPD – limited information)/Loss of consciousness/fever + PPD / Limited information to make any causality assessment
6	PPD / YES	PPD	PPD /Not reported	5/ #Unknown	Recovered	EEG/pleocytosis/ fever/ Limited information to make any causality assessment
7	PPD / YES	PPD	Not reported/Not reported	Unknown/ #Unknown	Recovered	EEG/pleocytosis/ fever/ Limited information to make any causality assessment
8	PPD / YES	PPD	Not reported/Not reported	Unknown/ #Unknown	Recovered	EEG/pleocytosis/ fever/ Limited information to make any causality assessment

Table 101 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment/Causality Assessment
9	PPD / YES	PPD	PPD / Not reported	Unknown/ #Unknown	/Unknown	fever > 1 day + Seizure +PPD +CSF >5 WBC; Pleocytosis; lymphocytosis + MRI findings (PPD

CSF Cerebrospinal Fluid, EEG Electroencephalogram, F Female, FLAIR Fluid-Attenuated Inversion Recovery, M Male, MRI Magnetic resonance imaging; LP Lumbar puncture; LGI Leucine-Rich Gliomain Activated, SA South Africa; UK United Kingdom; WBC White Blood Cells

Brighton Collaboration Level 3

Twenty-Six (26) out of 270 cases fulfilled Brighton collaboration level 3. These case reports are level 3 based on presence of one of the following factors: fever > 38.0°C, CSF pleocytosis, EEG changes consistent with encephalitis or brain neuroimaging consistent with encephalitis, with evidence of acute inflammation or demyelination and other diagnosis for illness could not be confirmed including neoplasm, toxic or metabolic encephalopathy, trauma or vascular disorder (Law B 2021 [C]). The cases are summarized below in Table 102.

Eighteen (18) case reports were reported in females and 8 were reported in males. The age range was 23-83 years.

The risk factors/ confounding factors included risk factor such Crohn's disease, Sjogren's syndrome, hypothyroidism, epilepsy, type 2 diabetes, hypertension, asthma, antiphospholipid syndrome, autoimmune hypothyroidism, lupus erythematosus disseminated, syndrome sicca and pyelonephritis.

Out of these 26 cases, the TTO from vaccination was missing in 4 cases. The median TTO was 8 days. In most of the cases there was limited information to make any causality assessment or presence of confounding factors.

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
1	PPD / YES	PPD	PPD	14 (1st Dose)	Not recovered	Possible PPD, H. zoster reactivation; would be infective due to zoster / Alternative causal factors noted
2	PPD / YES	PPD		8 (1st Dose)	Not recovered	Pre-existing PPD; thyroid disease; metabolic/ hepatic suggested by limited history. Seizures. Steroid use in two formulations may allow overdosing. PPD consistent with steroid induced PPD / Alternative causal factors noted
3	PPD / YES	PPD	Not provided	9 (1st Dose)	Not recovered	Extensive signs and symptoms but limited workup / Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
4	PPD / YES	PPD	Not provided	< 1 (1st Dose)	Not recovered	Negative CSF for viral cause. Process to PPD started day of vaccination. Appears to be PPD progression of events, details are lacking / Limited information to make an assessment
5	PPD / YES	PPD	PPD	1 (1st Dose)	Not recovered	Limited information to make an assessment
6	PPD / YES	PPD	Nonrelevant	1 (1st Dose)	Unknown	Evaluations are not available/ Limited information to make assessment.
7	PPD / YES	PPD	PPD	1 (Unknown)	Not recovered	Diagnostics not available; PPD ; benefit of doubt related to CSF results obtained but not presented. Might they show pleocytosis? The CSF is not noted to rule out encephalitis. Results may become available / Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
8	PPD / YES	PPD	Not provided	6 (1st Dose)	Recovering	Fever associated with sleepiness; PPD (unclear what elements); PPD / Limited information to make an assessment
9	PPD / YES	PPD	PPD	1 (1st Dose)	Recovering	Reactivation of Epstein Barr virus noted in narrative. Likely causative for encephalitis / Alternative causal factor noted
10	PPD / YES	PPD		Unknown/ (1st Dose)	Recovering	3+ weeks TTO; Results of EEG, CSF, imaging not provided / Limited information to make an assessment
11	PPD / YES	PPD	Not provided	Unknown/ (1st Dose)	Unknown	No specific inflammatory results except increased protein / Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
12	PPD / YES	PPD	PPD	62 (1st Dose)	Not recovered	Likely new infectious process started 2 months after vaccination / Alternative causal factors noted.
13	PPD / YES	PPD		19 (1st Dose)	Recovering	Fever/ PPD Other confounders reported such as lymphadenopathy, PPD, Lymphopenia and thrombocytopenia. Limited information regarding baseline conditions and work-up information to support the diagnosis and make an assesment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
14	PPD / YES	PPD	Not provided	21 (1st Dose)	Recovering	Seizure, fever, confusion; encephalitis evaluation unclear; cardiac and/or respiratory arrest required intubation. PPD encephalopathy may have had a role in the event / Limited information to make an assessment
15	PPD / YES	PPD	Not provided	10 (1st Dose)	Recovering	Treatment with PPD seemed to improve the condition / Limited information to make an assessment
16	PPD / YES	PPD	PPD	7 (1st Dose)	Unknown	Prolonged confusion, decreased mobility for at least PPD / Limited information to make an assessment
17	PPD / YES	PPD	Not provided	1 (1st Dose)	Recovered with sequelae	Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
18	PPD / YES	Unknown/ PPD	Not provided	Unknown (Unknown)	Not recovered	Work up results unknown, PPD . Associated with meningismus, fever; PPD , encephalitis / Limited information to make an assessment
19	PPD / YES	PPD	PPD	7 (2nd Dose)	Not recovered	Event occurred 7 days after second dose: autoimmune encephalitis due to LGI-1 antibody / Alternative causal factors noted
20	PPD / YES	PPD		12 (1st Dose)	Died	Autopsy results may help. Unclear what CSF showed, no results sent forward. Image appears to have shown PPD / Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
21	PPD / YES	PPD	Not provided	9 (1st Dose)	Recovered	CSF findings, not reported / Limited information to make an assessment
22	PPD / YES	PPD	PPD	Unknown (1st Dose)	Recovering	PPD consistent with PPD followed by or preceded by PPD on MRI, underlying PPD with encephalitis, consistent with PPD / Alternative causal factors noted
23	PPD / YES	PPD	Not provided	Unknown (1st Dose)	Not recovered	Thyroiditis causally may produce similar picture / Alternative causal factors noted
24	PPD / YES	PPD	Not provided/Not provided	10-14 (1st Dose)	Recovering	Sign of infection fever and PPD / Limited information to make an assessment

Table 102 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment / Causality Assessment
25	PPD / YES	PPD	PPD / Not provided	17 (1st dose)	Unknown	Pleocytosis / PPD / Limited information to make an assessment
26	PPD / YES	PPD	PPD / Not provided	17 (1st dose)	Ongoing	PPD and Pleocytosis / Limited information to make an assessment

COPD Chronic obstructive pulmonary disease, CSF Cerebrospinal Fluid, EEG: Electroencephalography, F Female; LGI Leucine-Rich Gliomain Activated, M Male; MRI Magnetic resonance imaging, TTO Time to onset; UK United Kingdom

Brighton Collaboration Level 4

Based on the review, 140 out of 270 cases were classified as Brighton collaboration level 4. These cases did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the cases.

Brighton Collaboration Level 5

Based on the review, 95 out of 270 cases were classified as Brighton collaboration level 5 (ie, Encephalitis excluded due to an alternative diagnosis).

Generally, there was too limited information in many case reports to make an informed assessment of causality or conclude on the presence of confounding factors.

Fatal cases

There were 8 case reports identified with fatal outcome. Summaries of these case reports with details are presented in Table 103 below.

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
1	PPD /Y/Spontaneous	BC5	PPD	34	28 / (Dose 1)	PPD , anaphylactic shock / Yes	Reported SAE verbatim: PPD (Preferred term: Encephalitis) Autopsy result was not provided however provisional diagnosis suggested that patient suffered PPD due to anaphylactic shock (severe allergic reaction) painkiller injection, PPD which is considered as an alternative cause for the event.
2	PPD /Y/Spontaneous	BC5		38	2 / (Dose 1)	Autoimmune encephalopathy; Myocardial ischaemia; Diabetes mellitus; Hypertension / Unknown	Reported verbatim: PPD (Preferred term: Autoimmune encephalopathy). Alternative causality: PPD ; patients with

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
							PPD
3	PPD /Y/Spontaneous	BC5	PPD	3	1 / (Dose 1)	PPD ; Arrhythmia; Acute myocardial infarction / Yes	Reported verbatim: PPD . (Preferred term: PPD) Alternative causality are the confounders (Arrhythmia; Acute myocardial infarction) and age as a risk factor. Insufficient information on etiological factors, relevant lab details and autopsy details. Autopsy result reported was not provided but cause cause of death was reported as PPD in anterior infraction with malignant rhythm disturbance, heart attack with resuscitation, PPD . Limited information

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
							to support diagnosis and make assessment.
4	PPD /N/Spontaneous	BC3	PPD	Unknown	11 / (Dose 1)	Encephalitis /Pending	Reported verbatim: PPD (Preferred term: Encephalitis). Autopsy result was pending which would be helpful in making an assessment. The cause of death was reported as PPD Lack of information on the status of ongoing COPD if it was actively exacerbated during this period. Unclear what CSF showed, no results sent forward. Image appears to have shown PPD and fever up to 38.5 degree Celsius makes this a BC3

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
5	PPD /N/Spontaneous	BC5	Not Mentioned	15	Unknown (Dose 1)	Cerebrovascular accident; PPD Cerebral venous thrombosis; Thrombocytopenia; Partial seizures; PPD ; Brain oedema / Unknown	Reported verbatim: PPD (Preferred term: PPD). Unknown TTO, limited info, limited diagnostic-work up information. Alternative causality are cerebral vascular accident, cerebral venous thrombosis with thrombocytopenia
6	PPD /Y/Spontaneous	BC5	PPD	17	Unknown / (Dose 1)	Cerebral venous sinus thrombosis; Pulmonary embolism; Seizure; Aneurysm; Hemorrhage; Thrombocytopenia; Arterial thrombosis;	Reported verbatim: PPD (Preferred term: Noninfective encephalitis). Autopsy result was not provided. The cause of death was reported as sinus vein thrombosis, pulmonary embolism/peripheral pulmonary embolism, seizure attack/generalized seizure,

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
						PPD / Yes	aneurysm, new onset sagittal sinus vein thrombosis with left partial occlusion and now pronounced venous congestion and left parietal congestive hemorrhage/extensive PPD, thrombocytopenia, and thrombosis in the peripheral pulmonary arteries. Limited info on etiological factors, autopsy reports, lab details, TTS might be confounding factor for the event outcome.
7	PPD /Y/Spontaneous	BC4	PPD	17	3 (Dose 1)	PPD / Unknown	Reported verbatim: PPD (Preferred term: Encephalitis). Limited info, nil work up info provided. Baseline conditions of cardiovascular disease (hypertension and dyslipidemia) risk factor of

Table 103 Summary of cases with fatal outcome for Encephalitis (n = 8)

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ Causality Assessment
							being a PPD. Was also on steroid which could contribute to immune compromise. Cause of death was listed as PPD. Limited information of course of events to support the diagnosis and make a causality assesment
8	PPD /Y/Spontaneous	BC4	Not Mentioned	Unknown	Unknown (Dose 1)	Encephalitis / Unknown	Reported verbatim: PPD (preferred term: Encephalitis). Limited info, limited work up info, limited medical history to support diagnosis and make assessment

ADEM Acute Disseminated Encephalomyelitis, BC Brighton Collaboration, COPD Chronic Obstructive Pulmonary Disease, CSF Cerebrospinal Fluid, F Female; M Male; N No; SAE Serious Adverse Event, TTO Time To Onset, TTS Thrombosis With Thrombocytopenia Syndrome, Y Yes

Summary of Fatal case reports

Out of 8 case reports 5 were wrongly coded to Encephalitis or Encephalopathy. These reported verbatim included: severe consecutive increasing brain, hypoxic brain damage, acute disseminated encephalitis (ADEM), hypoxic-ischemic encephalopathy, and encephalogic death.

Of the 8 case reports, the cause of death for 4 were reported as not related to Encephalitis or Encephalopathy, 3 were not provided and only 1 had encephalitis listed as cause of death.

Out of 8 case reports 4 were within risk window of 2-42 days, 1 was outside the risk window and remaining 3 were unknown. One of the 8 case reports (PPD) was assessed as a BC3 and Possibly related with limited information using WHO-UMC classification. In this case report, the TTO was 11 days, which was within the risk window. However, there was lack of information and clarity on available supportive diagnostics (ie, cerebrospinal fluid culture, MRI results), course of events and pending autopsy result. the available information in this report was limited with lack of clarity. Two (2)case reports were assessed as BC5 based on alternative causalities as confounders or baseline conditions of the patients before the onset of the event. Lack of autopsy results also make it difficult to make causality assessment on these case reports.

In conclusion, the review of these 8 case reports with fatal outcome did not identify definitive causal association between Encephalitis and COVID-19 Vaccine AstraZeneca.

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of encephalitis is presented with different risk windows (14 days, 30 days, and 42 days) in Table 104. This includes all reported cases irrespective of the Brighton collaboration criteria level. The risk window of 2-42 days was included from the Brighton case definition (Law B 2021 [C]). As a conservative approach, cases with time to onset within 2 days were included in the analysis. Where not otherwise stated, cases with unknown time to onset were excluded from the analysis. The background incidence rates used are from Willame et al 2021 [B] and from Granerod et al 2013. The outcome of observed versus expected analysis of all cases for encephalitis suggested that observed cases were less than expected. The observed versus expected analysis of cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all age stratifications in EEA/UK. Most cases in all age groups from EEA/UK showed insufficient information to make any causality assessment and only few cases met the Brighton Collaboration Criteria Level 1, 2 or 3. These cases showed that observed cases occurred significantly less frequently than expected.

Table 104 Observed Versus Expected Analysis for all cases reporting encephalitis (Global reports)

Adverse Events	Risk window	IR	Exposure[a]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
Overall Incidence Rate Encephalitis	14	9.1	291626957	106	1017.22	0.1 (0.09 - 0.13)	Observed significantly < expected
Overall Incidence Rate Encephalitis	30	9.1	291626957	132	2179.76	0.06 (0.05 - 0.07)	Observed significantly < expected
Overall Incidence Rate Encephalitis	42	9.1	291626957	139	3051.67	0.05 (0.04 - 0.05)	Observed significantly < expected
Overall Incidence Rate Encephalitis cases	42 + Unknown	9.1	291626957	238	3051.67	0.08 (0.07 - 0.09)	Observed significantly < expected

[a] Exposure until 28 December 2021; Incidence rate (IR) = 9.1/100,000 person years. Source: Willame et al 2021 [B] Median IR from CPRD (UK;2019); ARS (Italy; 2019); BIFAP PC/HOSP (Spain, 2018)

CI Confidence Interval, E Expected, IR Incidence rate, O Observed

An observed versus expected analysis of cases meeting case definition according to Brighton Criteria for Level 1, 2 or 3, based on clinical course, examination such as brain histopathology, clinical features, and evaluations (Law B 2021 [A]) are presented in Table 105.

Table 105 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,0 00 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis Age 18-49	14	7.48	27716022	40	79.47	0.5 (0.36 - 0.69)	Observed significantly < expected

Table 105 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,0 00 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis Age 18-49	30	7.48	27716022	47	170.28	0.28 (0.2 - 0.37)	Observed significantly < expected
EEA UK Encephalitis Age 18-49	42	7.48	27716022	48	238.4	0.2 (0.15 - 0.27)	Observed significantly < expected
EEA UK Encephalitis Age 50-59	14	8.66	19552392	14	64.9	0.22 (0.12 - 0.36)	Observed significantly < expected
EEA UK Encephalitis Age 50-59	30	8.66	19552392	18	139.08	0.13 (0.08 - 0.2)	Observed significantly < expected
EEA UK Encephalitis Age 50-59	42	8.66	19552392	22	194.71	0.11 (0.07 - 0.17)	Observed significantly < expected
EEA UK Encephalitis Age 60-69	14	9.87	28510714	22	107.86	0.2 (0.13 - 0.31)	Observed significantly < expected
EEA UK Encephalitis Age 60-69	30	9.87	28510714	31	231.13	0.13 (0.09 - 0.19)	Observed significantly < expected
EEA UK Encephalitis Age60-69	42	9.87	28510714	31	323.59	0.1 (0.07 - 0.14)	Observed significantly < expected
EEA UK Encephalitis Age 70-79	14	11.95	14795684	11	67.77	0.16 (0.08 - 0.29)	Observed significantly < expected
EEA UK Encephalitis Age 70-79	30	11.95	14795684	11	145.23	0.08 (0.04 - 0.14)	Observed significantly < expected
EEA UK Encephalitis Age 70-79	42	11.95	14795684	12	203.32	0.06 (0.03 - 0.1)	Observed significantly < expected

Table 105 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,0 00 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis Age 80+	14	8.47	3858135	3	12.53	0.24 (0.05 - 0.7)	Observed significantly < expected
EEA UK Encephalitis Age 80+	30	8.47	3858135	3	26.84	0.11 (0.02 - 0.33)	Observed significantly < expected
EEA UK Encephalitis Age 80+	42	8.47	3858135	3	37.58	0.08 (0.02 - 0.23)	Observed significantly < expected

[a] Source: Willame et al 2021 [B] Median IR from CPRD (UK;2019); ARS (Italy; 2019); BIFAP PC/HOSP (Spain, 2018)

[b] Exposure until 28 December 2021 for EEA/UK

CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom

An observed versus expected analysis of cases meeting case definition according to Brighton Criteria for Level 1, 2 or 3 was presented in Table 106.

Table 106 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis BC 1-3 Age 18 to 49	14	7.48	27716022	6	79.47	0.08 (0.03 - 0.16)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 18 -49	30	7.48	27716022	10	170.28	0.06 (0.03 - 0.11)	Observed significantly < expected

Table 106 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis BC 1-3 Age 18 -49	42	7.48	27716022	10	238.4	0.04 (0.02 - 0.08)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 50-59	14	8.66	19552392	0	64.9	0 (0 - 0.06)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 50-59	30	8.66	19552392	0	139.08	0 (0 - 0.03)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 50-59	42	8.66	19552392	0	194.71	0 (0 - 0.02)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 60-69	14	9.87	28510714	3	107.86	0.03 (0.01 - 0.08)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 60-69	30	9.87	28510714	4	231.13	0.02 (0 - 0.04)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 60-69	42	9.87	28510714	4	323.59	0.01 (0 - 0.03)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 70-79	14	11.95	14795684	2	67.77	0.03 (0 - 0.11)	Observed significantly < expected

Table 106 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions

Age group	Risk window	IR[a] /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK Encephalitis BC 1-3 Age 70-79	30	11.95	14795684	2	145.23	0.01 (0 - 0.05)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 70-79	42	11.95	14795684	2	203.32	0.01 (0 - 0.04)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 80	14	8.47	3858135	1	12.53	0.08 (0 - 0.44)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 80	30	8.47	3858135	1	26.84	0.04 (0 - 0.21)	Observed significantly < expected
EEA UK Encephalitis BC 1-3 Age 80	42	8.47	3858135	1	37.58	0.03 (0 - 0.15)	Observed significantly < expected

[a] Willame et al 2021 [B] Median IR from CPRD (UK;2019); ARS (Italy; 2019); BIFAP PC/HOSP (Spain, 2018)

[b] Exposure until 28 December 2021 for EEA/UK.

CI Confidence Interval, E Expected, EEA European Economic Area; IR Incidence rate, O Observed PY Person Years; TTO Time to onset; UK United Kingdom.

Literature

A literature search through 28 December 2021 was conducted in the Embase and InsightMeme database to review the occurrence of Encephalitis in association with vaccines, other COVID Vaccines and COVID-19 infection. The search yielded 45 articles, of which 2 included 4 cases of encephalitis with COVID-19 VACCINE ASTRAZENECA, included in the review above (PPD).

There were no articles identified which discussed a possible mechanism of action between encephalitis and COVID-19 VACCINE ASTRAZENECA.

Summary

Of 270 cases, 183 (67.8%) of vaccinees were from the age group of 18-<65(adult) and median age was found to be 57 years, there was not a predominant stratification in gender. In 233 (86.3%) cases, the events were reported to have occurred after the first dose, 21(7.78%) case reports after the second dose of vaccine, no events were reported with booster dose and dose was not reported in 16 (5.93%) case reports. The Median TTO for all the cases was found to be 9 days. 139 (51.5%) out of 270 cases were within the risk window of 2-42 days. 265 (98.1%) of 270 cases were serious. The review of 8 case reports with fatal outcome did not identify any evidence of a causal association between Encephalitis and COVID-19 Vaccine AstraZeneca. No changes were identified for interval data and cumulative data considering both safety patterns and volumes. Based on Brighton Collaboration criteria approach, out of the 270 cases, 9 fulfilled level 2 criteria, 26 fulfilled level 3 criteria, 140 fulfilled level 4 criteria and 95 cases fulfilled level 5 criteria. 63 (23.3%) cases were evaluated with Alternative causal factors noted and the remaining cases were evaluated with limited information to make any causality assessment. The review of post authorization case reports did not find any evidence of a causal association between Encephalitis and COVID-19 Vaccine AstraZeneca. The observed versus expected analysis of all cases for encephalitis suggested that observed cases were less than expected. The observed versus expected analysis of cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all age stratifications in EEA/UK. On further review of cases in all age groups from EEA/UK showed that most cases had insufficient information to make any causality assessment and only few cases met the Brighton Collaboration Criteria Level 1, 2 or 3. O/E analysis for cases of encephalitis in this age group based on Brighton Collaboration Criteria Level 1, 2 or 3 showed that observed cases occurred significantly less frequently than expected.

Conclusion

Based on the currently available information, AstraZeneca did not find evidence of a new or emerging signal to suggest a need to update the product information. Surveillance of

encephalitis will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the AESI of Nervous system disorders, including immune-mediated neurological conditions.

16.3.1.1.3 Transverse Myelitis

Request

AstraZeneca received the following request from PRAC in the AR for the 8th SSR (review periods: 01 October 2021 – 30 November 2021):

"Transverse myelitis: the MAH should continue the monitoring of transverse myelitis and provide an updated review of new data from post-marketing and literature."

AstraZeneca's response to this request is provided below.

Review of Cases

Interval Period (29 June 2021 – 28 December 2021)

A search of the AstraZeneca safety database was conducted for the reporting period data (29 June 2021 to 28 December 2021) using the following MedDRA PTs: Myelitis transverse, Myelitis, and Acute necrotizing myelitis with COVID-19 VACCINE ASTRAZENECA.

The search identified 152 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 152 cases: 5 of the cases are literature reports; 1 case is a non-interventional / post-market report; 145 cases are spontaneous report(s); 1 case (PT: myelitis transverse) is from the active arm of clinical study COV002. There were no reports of transverse myelitis from the other Oxford studies (COV001, COV003, C0V005). Overall, there is no imbalance for transverse myelitis in the pooled COV clinical studies. There were no reports of transverse myelitis from AZ sponsored studies (D8110C00001 and D8111C00002).

Out of the 152 cases: 146 (96.1%) of the cases were serious and 47 (30.9%) were medically confirmed. There were no fatal reports.

Out of the 152 reports, 64 (42.1%) were from the United Kingdom (UK) including 1 clinical study case, 32 (21.1%) from Germany, 13 (8.6%) from Australia, 10 (6.6%) from Brazil, 6 (3.9%) from India, 4 (2.6%) from France, 3 (2.0%) each from Italy and the Netherlands, 2 (1.3%) each from Guatemala, Mexico, Sweden and the United States, 1 (0.7%) each from [redacted]

There were 83 (54.6%) reports in female vaccinees, 67 (44.1%) were in male vaccinees and the gender was not reported in 2 cases (1.3%). The age range was 20-83 years

of age with a median age of 52 years. 108 (71.1%) vaccinees were in the age group of 18-<65 years of age, 25 (16.4%) vaccinees were >65 years of age, and for 14 (9.2%) vaccinees the age was unknown.

The adverse events reported included Myelitis transverse (95 PTs), Myelitis (62 PTs). An individual case report can have more than one of the above events reported.

Out of the 152 cases, 92 had the time to onset (TTO) within 42 days, and in 39 cases the TTO was unknown. The median TTO was 12 days (range 0-150 days). One case from regulatory authority reported TTO as 387 days which may be considered a miscoding. Out of the 152 cases, 75 (49.3%) reported the event occurring after the first dose, 25 (16.4%) reported the event occurring after the second dose. For 53 cases the dose number was not specified.

Out of the 152 cases, 12 (7.9%) recovered, 28 (18.4%) were recovering, 1 (0.7%) recovered with sequelae, 92 (60.55) had not recovered and for 19 (12.5%) cases the outcome was unknown. No cases had a fatal outcome.

Cumulative Review through 28 December 2021

A cumulative search through of the AstraZeneca global patient safety was conducted through 28 December 2021 using the same search strategy described above.

The search identified 260 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 260 cases: 9 of the cases are literature reports; 1 case is a non-interventional / post-market report; 249 cases are spontaneous report(s); 1 case (PT: myelitis transverse) is from the active arm of clinical study COV002. Transverse myelitis was observed twice in the control arm (PT: Myelitis transverse and PT: Myelitis) and once in the AZD1222 arm (PT: Myelitis transverse) in the COV002 study. There were no reports of transverse myelitis from the other Oxford studies (COV001, COV003, C0V005). Overall, there is no imbalance for transverse myelitis in the pooled COV clinical studies. There were no reports of transverse myelitis from AZ sponsored studies (D8110C00001 and D8111C00002).

Out of the 260 cases: 241 (92.7%) of the cases were serious and 103 (39.6%) were medically confirmed. There was one fatal report (PPD), which is discussed below.

Out of the 260 reports, 132 (50.8%) were from the United Kingdom (UK) including 1 clinical study case, 36 (13.8%) from Germany, 13 (5.0%) from Australia, 11 (4.3%) from Brazil, 10 (3.8%) from France, 7 (2.7%) each from India, Italy and the Netherlands, 5 (1.9%) each from Spain and Sweden, 3 (1.2%) from the republic of Korea, 2 (0.8%) each from Austria, Croatia, Guatemala, Ireland, Mexico, Portugal and the United States, 1 (0.4%) each from [redacted]

There were 144 (55.4%) reports in female vaccinees, 110 (42.3%) were in male vaccinees and the gender was not reported in 6 cases (2.3%). The age range was 16-88 years of age with a median age of 50 years. 177 (68.1%) vaccinees were in the age group of 18-<65 years of age, 45 (17.3%) vaccinees were >65 years of age, 1 (0.4%) vaccinee was <18 years of age and for 33 (12.7%) vaccinees the age was unknown.

The adverse events reported included Myelitis transverse (173 PTs), Myelitis (93 PTs). An individual case report can have more than one of the above events reported.

Out of the 260 cases, 161 had the time to onset (TTO) within 42 days, and in 77 cases the TTO was unknown. The median TTO was 10 days (range 0-150 days). One case from regulatory authority reported TTO as 387 days which may be considered a miscoding. Out of the 260 cases, 141 (54.2%) reported the event occurring after the first dose, 29 (11.1%) reported the event occurring after the second dose. For 90 (34.6%) cases the dose number was not specified.

Out of 260 reports received to date, 1 case has been reported with a fatal outcome. The cause of death was reported as myelitis transverse, however autopsy report was not available (see Table 107). Based on information provided, this is not a true case of transverse myelitis. MHRA has confirmed after a series of background checks, the fatal TM case had been nullified in their systems as it was deemed a non-valid (fake) report. However, as this case is still in the AstraZeneca safety database it is presented here below.

Table 107 Summary of case with fatal outcome for Transverse myelitis

No	Case ID/ Country/ Age/Gender	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/Autopsy (Y/N)	Additional Comment/ Causality Assessment
1	PPD / Unknown / PPD	BC4	Unknown	4	4 (Dose 1)	Myelitis Transverse/ N	Four days after vaccination patient died; unclear if case definition for TM was met. Deemed as a non-valid (fake) case by MHRA.

BC Brighton Collaboration; MHRA Medicines and Healthcare Products Regulatory Agency; N No; TM Transverse Myelitis; UK United Kingdom; Y Yes.

The BCC (Law B 2021 [C]) was used for the review of the data available in the case reports. Based on this approach, out of the 260 cases: None of the cases fulfilled BCC Level 1 criteria; 10 cases fulfilled BCC Level 2 criteria; 34 cases fulfilled BCC Level 3 criteria; 209 cases fulfilled BCC Level 4 criteria; 7 cases fulfilled BCC Level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for Acute Myelitis (Law B 2021 [C]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, comorbidities, infections, vaccines and malignancies).

BCC Level 1 for Transverse myelitis

None of the 260 cases fulfilled BCC Level 1 criteria according to classification by clinical course, examination features and/or level of certainty, based on algorithm in Law B 2021 [C].

BCC Level 2 for Transverse myelitis

Ten out of the 260 case reports fulfilled BCC level 2 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory and are presented in Table 108.

Out of these 10 cases, 2 reports were reported in females and 8 were reported in males and the age range was 32-61 years. The median age was 45 years.

All of the 10 cases had time to onset from vaccination within 42 days. The median time to onset was 10 days.

Out of these 10 cases, 5 cases reported to have occurred after receiving the first dose, and the remaining 5 after “unknown” dose. Out of the 10 cases fulfilling BCC Level 2, 8 cases had been assessed as Possible, 1 case as Probable/likely and remaining 1 case as unlikely as per WHO-UMC Causality assessment criteria.

Table 108 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N=10)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
1.	PPD YES	Unk/PPD	Unk/Unk	Unknown/3 days	Myelitis/Recovering	Possible	TTO: 3 days, LP with elevated protein, absence of bacterial, elevated leucocytes, no other details regarding possible infections
2.	PPD YES	PPD	PPD /Unk	1st dose/9 days	Myelitis/Recovering	Possible	Migraine history; no etiological work up, no infectious work up, family. CSF studies had limited information. MRI suggested PPD
3.	PPD /YES	PPD	Unk/PPD	Unknown/14 days	Myelitis transverse/Unknown	Possible	Increasing lymphocytosis in CSF since treatment; Etiologic work up limited. Paraneoplastic process should be eliminated with progressive lymphocytosis.

Table 108 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N=10)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
4.	PPD /YES	PPD	Unk/Unk	1st dose/16 days	Myelitis transverse/Not recovered	Possible	B 12 myelopathy, also PPD noted, also suspicion of PPD due to prolonged evolution of PPD with ongoing swelling
5.	PPD YES	PPD	Unk/Unk	Unknown/10 days	Myelitis transverse/Not recovered	Possible	Aetiology and diagnostic work up not known.
6.	PPD /YES	PPD	PPD	1st dose/11 days	Myelitis transverse/Recovering	Probable-Likely	Lacks info on co-morbidities, past medical history, previous travel, lifestyle, risk factors. CSF consistent with infective meningitis.
7.	PPD YES	PPD		Unknown/17 days	Myelitis transverse/Recovering	Possible	Aetiology and diagnostic work up not known.
8.	PPD /YES	PPD	PPD /Unk	1st dose/14 days	Myelitis transverse/Recovered	Possible	TTO: 2 weeks, medical history included PPD. MRI contrast enhanced of the spine revealed PPD . CSF: pleocytosis, and mild elevated protein levels.

Table 108 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N=10)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors -Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							The tumour marker and autoimmune profiles, including the serum rheumatoid factor, serum complement C3 and C4, anti-Ro/La antibody, antinuclear antibody, and anti-ds-DNA antibody, were all in the normal range. However, PPD . No other laboratory, no fever
9.	PPD /YES	PPD	PPD /Unk	Unknown/8 days	Myelitis transverse/Recovering	Possible	Not sufficient information regarding etiological work up, infectious work up, family unknown.
10.	PPD /YES	PPD	PPD	1st dose/1 days	Myelitis transverse/Not recovered	Unlikely	Pre-existing MS, onset of TM in less than 12 hours after vaccination suggests pathogenesis was underway at the time of vaccination.

CSF Cerebrospinal fluid, F Female, M: Male, MRI Magnetic Resonance Imaging, TM Transverse Myelitis, TTO Time To Onset.

BCC Level 3 for Transverse Myelitis

34 out of the 260 case reports fulfilled BCC level 3 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory and are presented in Table 109.

Out of these 34 cases, 24 reports were reported in females and 10 were reported in males and the age range was 20-74 years. The median age was 46 years. Out of these 34 cases, time to onset from vaccination was beyond 42 days in 3 of the cases and missing in 10 of the cases. The median time to onset was 12 days.

In 6 of the cases the event was reported to have occurred after receiving the second dose.

Out of the 34 cases fulfilling BCC Level 3, 24 cases had been assessed as Possible, 6 cases as Conditional/Unclassified, and 4 cases as Unlikely as per WHO Causality assessment criteria.

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
1.	PPD /YES	PPD	Unk/Unk	1st dose/ 49 days	Myelitis/ Not recovered	Unlikely	49 d TTO is beyond the typical risk window; Diagnoses noted are conflicting: PPD, vs. transverse myelitis; infectious, vs. autoimmune, vs MS, vs PPD. Coding is conflicting. Additional diagnostics would be helpful to help with causality. Aetiology and diagnostic work up not known. MS or other pre-existing disorder not known. Family and medical history would be helpful.
2.	PPD /YES	PPD	Unk/PPD	Unknown / Unknown days	Myelitis transverse/ Not recovered	Unassessable/ Unclassifiable	TTO: unknown, no medical history, MRI confirmed diagnosis, however, no details regarding results or information about study
3.	PPD /YES	PPD	PPD /Unk	1st dose / 0 days	Myelitis transverse/ Not recovered	Unlikely	Aetiology and diagnostic work up not known.
4.	PPD /YES	PPD	Unk/PPD	1st dose / Unknown days	Myelitis transverse/ Not recovered	Unassessable/ Unclassifiable	story of pre-existing TM, with similar symptoms.
5.	PPD /YES	PPD	Unk/Unk	Unknown/Unknown days	Myelitis/ Not recovered	Unassesable/ Unclassifiable	Aetiology and diagnostic work up not known. The case is confounded by metastatic prostate cancer.

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
6.	PPD /YES	Unk/PPD	Unk/Unk	Unknown/Unknown days	Myelitis transverse/ Unknown	Unassesable / Unclassifiable	long TTO after vaccination; other aetiology not discussed however limited information on diagnostic and aetiology work up provided.
7.	PPD /YES	PPD	PPD	Unknown/Unknown days	Myelitis transverse/ Not recovered	Unassesable / Unclassifiable	Aetiology and diagnostic work up not known.
8.	PPD /YES	PPD	Unk/Unk	1st dose/ Unknown days	Myelitis transverse/ Not recovered	Unassesable / Unclassifiable	Unknown TTO. Unknown past medical or family history or work up.
9.	PPD /YES	PPD	Unk/PPD	2nd dose/ Unknown days	Myelitis transverse/ Recovering	Unassesable / Unclassifiable	unknown vaccination product. Unknown TTO. Past medical history, current co-morbidities, current medications and diagnoses unknown.
10.	PPD /YES	PPD	Unk/Unk	1st dose/ Unknown days	Myelitis transverse/ Recovering	Unassesable / Unclassifiable	Aetiology and diagnostic work up not known. No medical or drug history.
11.	PPD /YES	PPD	Unk/Unk	1st dose/ 16 days	Myelitis transverse/ Recovering	Possible	No medical history, no details about aetiology, no details regarding fever more than 48 h after vaccination. CSF no reporting pleocytosis

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
12.	PPD /YES	PPD	Unk/Unk	1st dose/ 11 days	Myelitis/ Recovering	Possible	TTO:11 days, Aetiology and diagnostic work up not known. MS or other pre-existing disorder not known. Family and medical history would be helpful.
13.	PPD /YES	PPD	PPD /Unk	2nd dose/ 58 days	Myelitis/ Recovering	Unlikely	TTO: 58 days, MRI brain reported, PPD . No malignancies founded. HIV, LUES, CMV, EBV, negative.
14.	PPD /YES	PPD	PPD /Unk	2nd dose/ 28 days	Myelitis/ Recovering	Possible	TTO: 28 days, patient who also experienced oral herpes, MRI whole spine- PPD CT brain- NAD Patient had LP with the following results- Negative Gram Stain less than 1 White cell 4 Red Cells Protein 1.09 Glucose 4.1 (serum was 6.8) Lyme, syphilis and HIV serology negative, ACE negative CSF culture negative
15.	PPD /YES	PPD	PPD /Unk	Unknown/9 days	Myelitis/ Not recovered	Possible	work up, comorbidities, past medical and family histories not available.
16.	PPD /YES	PPD	Unk/Unk	Unknown/14 days	Myelitis/Recovered with sequelae	Possible	no etiological work up, past medical or family history taken. Little info except MRI findings and PPD

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
17.	PPD YES	PPD	Unk/Unk	Unknown/3 days	Myelitis/Not recovered	Possible	CSF with pleocytosis, Mild, results not further available. No optic neuritis: diagnostics for cervical myelitis not noted here.
18.	PPD /YES	PPD	Unk/Unk	2nd dose/ 12 days	Myelitis/ Not recovered	Possible	limited suspicion on MRI spine; no other inflammation.
19.	PPD /YES	PPD	Unk/PPD PPD	Unknown/2 days	Myelitis transverse/ Not recovered	Possible	Comorbidities of arthritis, fibromyalgia, auto immune relatedness
20.	PPD /YES	PPD	PPD /Unk	1st dose/ 20 days	Myelitis transverse/ Not recovered	Possible	TTO: 20 days, Medical history included Multiple sclerosis. PPD, MRI showed PPD PPD
21.	PPD /YES	PPD	PPD	1st dose/ 18 days	Myelitis transverse/ Not recovered	Possible	Aetiology and diagnostic work up not known. MS or other pre-existing disorder not known. Family and medical history would be helpful.
22.	PPD /YES	PPD	Unk/Unk	1st dose/ 11 days	Myelitis transverse/ Not recovered	Possible	work up not available, unknown co-morbidities, relevant history, relevant family history not available. 11 D TTO possibly.

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
23.	PPD /YES	PPD	PPD	1st dose/ 7 days	Myelitis transverse/ Not recovered	Possible	underlying diagnosis of MS with treatment with fingolimod
24.	PPD /YES	PPD	PPD /Unk	Unknown/21 days	Myelitis transverse/ Not recovered	Possible	Lacking examination of lesion, other findings besides sensory level; Does have spinal stenosis, unclear how contributory.
25.	PPD /YES	PPD	Unk/Unk	1st dose/ 9 days	Myelitis transverse/ Not recovered	Possible	TTO: 9 days, no medical history, no concomitant medications, Electroneuromyography, MMII: PPD Other conditions to be excluded such as Infections or autoimmune
26.	PPD /YES	PPD	Unk/PPD	1st dose/ 40 days	Myelitis transverse/ Not recovered	Possible	comorbidities, con meds, medical history not available; diagnostics not complete.
27.	PPD /YES	PPD	PPD	1st dose/ 25 days	Myelitis transverse/ Recovering	Possible	History previous diagnosis of PPD , or pre-existing stimulation for relapse

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
			PPD				
28.	PPD	PPD	PPD	Unknown/3 days	Myelitis transverse/	Possible	Aetiology, infectious, other co-morbidities, or disorders associated with TM are not known.

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
	PPD /YES		PPD /Unk		Not recovered		
29.	PPD /YES	PPD	Unk/Unk	1st dose/11 days	Myelitis transverse/ Recovered	Possible	medical history, family history, risks, co-morbidities, concomitant medications not known.
30.	PPD /YES	PPD	Unk/Unk	Unknown/Unknown days	Myelitis transverse/ Not recovered	Unassessable/ Unclassifiable	TTO: unknown, no medical history, no concomitant medications. COVID-19 PCR negative. Apparently, patient had same symptoms after 2nd dose, however, there is no details which symptoms patient had again, since after 1st dose, events reported were chest pain, pain in extremity, diarrhoea, headache. MRI confirmed TM, but no information about which details were found.
31.	PPD /YES	PPD	Unk/Unk	Unknown/13 days	Myelitis transverse/ Not recovered	Possible	limited suspicion on MRI spine; no other inflammation. Unknown etiological work up other than influenza like illness noted after vaccination.
32.	PPD /YES	PPD	Unk/PPD	2nd dose/ 150 days	Myelitis transverse/ Not recovered	Unlikely	TTO: 150 days, no medical history, patient receiving treatment for HTA, tachycardia and diverticulitis. TM confirmed by MRI, COVID-19 PCR negative, however there is no details regarding MRI results, just confirmation.

Table 109 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 34)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
33.	PPD /YES	PPD	PPD /Unk	1st dose/ 10 days	Myelitis transverse/ Not recovered	Possible	MRI shows inflammation/lesion in cervical cord. Exacerbation of PPD can involve the spinal cord.
34.	PPD /YES	PPD	PPD	2nd dose/ 29 days	Myelitis transverse/ Recovering	Possible	TTO 29 day for PPD Unclear if PPD is related to Myelitis. Aetiology work up unknown

CSF: Cerebrospinal Fluid, F Female, GBS: Guillain Barre Syndrome, M Male, MRI: Magnetic resonance imaging, NOMSD: Neuromyelitis Optica spectrum disorder, PT Preferred Term, TM: Transverse Myelitis, TTO Time to onset, UMC Uppsala Monitoring Centre, WHO World Health Organization

BCC Level 4 for Transverse Myelitis

A case was categorised as Brighton Collaboration Level 4 based on the absence of clinical history, examination and laboratory investigation results necessary to determine a level of diagnostic certainty based on algorithm in Law B 2021 [C].

A total of 209 cases fulfilled BCC Level 4 criteria, these cases did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the case. Limited information to make any causality assessment were noted in 190 of the cases, and alternative causal factors were noted in 19 of the cases.

BCC Level 5 for Transverse Myelitis

A case was categorised as Brighton Collaboration Level 5 for acute myelitis based on clinical history, examination, and laboratory investigation results to determine level of diagnostic certainty based on algorithm in Law B 2021 [C].

Seven (7) of the 260 case reports fulfilled BCC level 5 criteria. Six of the cases had unknown relevant risks and/or concomitant medications, while 1 case report was confounded by underlying cancer. Two out of these cases were found to be duplicates upon further review.

Case-level Review Summary

None of the cases of Transverse myelitis fulfilled BCC Level 1 criteria.

A total of 10 cases fulfilled BCC Level 2 criteria. Eight (8) cases of transverse myelitis assessed for WHO-UMC causality term as Possible, 1 case as Probable-likely and the remaining 1 as unlikely.

Two (2) of the 8 cases assessed as possible, were classified solely based on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as on vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc.) to rule out alternative explanations.

A total of 34 cases of transverse myelitis fulfilled BCC Level 3 criteria. Out of these 34 cases 23 were assessed by AstraZeneca according to WHO-UMC causality Possible, 6 cases were assessed as Conditional/ Unclassified, 4 cases were assessed as Unlikely and 1 case was assessed as Probable-likely. Seven (7) of the 23 cases assessed as Possible based solely on the TTO, however there was insufficient case information (such as on vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc.) for further evaluation.

A total of 209 cases fulfilled BCC Level 4 criteria and 7 cases fulfilled BCC Level 5 criteria. Two out of these cases were found to be duplicates upon further review.

Of the remaining cases, the event could also be explained by the vaccinees' diseases or other medications (Sarcoidosis, Devic's disease (Neuromyelitis Optica), Multiple sclerosis (necessitating treatment with fingolimod, CSF cell counts suggesting CSF infections, thrombosis milieu, pre-existing spinal stenosis suggesting pre-existing spinal pathologies, pre-existing immune and neuromuscular inflammatory milieu (as suggested by fibromyalgia, arthritis).

Observed Versus Expected Analysis

The observed versus expected analysis was carried out for cases of transverse myelitis with COVID-19 VACCINE ASTRAZENECA received through 28 December 2021. There were 260 cases, a total of 160 cases had the time to onset (TTO) within 42 days and in 80 cases, the TTO was unknown.

Willame et al 2021 [B] have as part of ADVANCE EUROPE given incidence rates for transverse myelitis, stratified by age (Willame et al 2021 [B]). the rates are slightly lower than other rates found corresponding to a more conservative estimate for background rates. An appendix to the same article by Willame et al 2021 [B] has given incidence rates stratified by age and gender.

Global overall rates based on the rates from ADVANCED Europe are presented in Table 110. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

The risk window for myelitis as a product related reaction for inactivated or subunit vaccines is likely similar to ADEM, where the recommended risk window for individuals is 2-42 days (Law B 2021 [B]. We have used the risk window of 42 days for this analysis, ie, cases that have the time to onset 42 days or less from receiving vaccine until the event occurred are counted in the observed numbers.

Table 110 Observed versus Expected Analysis for Transverse Myelitis Overall and for Brighton Collaboration Criteria Level 1 – 3 cases, both with and without known TTO

Age group/ Gender	Risk window (days)	Back-ground rates	Exposure[a]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall	42	0.97	291626957	160	325.29	0.49 (0.42 - 0.57)	Observed significantly < expected
Overall +Unk TTO	42	0.97	291626957	240	325.29	0.74 (0.65 – 0.84)	Observed significantly < expected
Overall BCC 1-3	42	0.97	291626957	31	325.29	0.1 (0.06 - 0.14)	Observed significantly < expected
Overall +Unk TTO BCC 1-3	42	0.97	291626957	41	325.29	0.13 (0.09 - 0.17)	Observed significantly < expected

[a] Exposure until 28 December 2021. All global reports are included in observed numbers. Exposure numbers are from United Kingdom, EEA, Australia, Canada, Philippines and Brazil. Exposure numbers from India are not included.

BCC Brighton collaboration criteria; CI Confidence Interval; TTO Time to onset; Unk Unknown.

Observed versus expected analyses stratified by age in the EEA and the UK, using rates from ADVANCED Europe (Willame et al 2021 [B]) are presented in Table 111. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 111 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the EEA/UK

Age group	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
15-24 years	42	0.64	2202670	6	1.62	3.7 (1.36 - 8.06)	Observed significantly > expected
25-44 years	42	1.36	25513352	43	39.9	1.08 (0.78 - 1.45)	Observed > expected

Table 111 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the EEA/UK

Age group	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
45-64 years	42	1.23	19552392	49	27.65	1.77 (1.31 - 2.34)	Observed significantly > expected
65 years +	42	0.76	47164533	27	41.22	0.66 (0.43 - 0.95)	Observed significantly < expected
15-24 years including cases with an unknown TTO	42	0.64	2202670	8	1.62	4.94 (2.13 - 9.73)	Observed significantly > expected
25-44 years including cases with an unknown TTO	42	1.36	25513352	56	39.9	1.4 (1.06 - 1.82)	Observed significantly > expected
45-64 years including cases with an unknown TTO	42	1.23	19552392	73	27.65	2.64 (2.07 – 3.32)	Observed significantly > expected
65 years + including cases with an unknown TTO	42	0.76	47164533	35	41.22	0.85 (0.59 - 1.18)	Observed < expected
15-24 years BC 1-3	42	0.64	2202670	2	1.62	1.23 (0.15 - 4.46)	Observed > expected

Table 111 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the EEA/UK

Age group	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years BCC 1-3	42	1.36	25513352	9	39.9	0.23 (0.1 - 0.43)	Observed significantly < expected
45-64 years BCC 1-3	42	1.23	19552392	10	27.65	0.36 (0.17 - 0.67)	Observed significantly < expected
65 years + BCC 1-3	42	0.76	47164533	1	41.22	0.02 (0 - 0.14)	Observed significantly < expected
15-24 years BCC 1-3 including cases with an unknown TTO	42	0.64	2202670	2	1.62	1.23 (0.15 - 4.46)	Observed > expected
25-44 years BCC 1-3 including cases with an unknown TTO	42	1.36	25513352	11	39.9	0.28 (0.14 – 0.49)	Observed significantly < expected
45-64 years BCC 1-3 including cases with an unknown TTO	42	1.23	19552392	14	27.65	0.51 (0.28 - 0.85)	Observed significantly < expected
65 years + BCC 1-3 including cases with an	42	0.76	47164533	3	41.22	0.07 (0.02 - 0.21)	Observed significantly < expected

Table 111 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the EEA/UK

Age group	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
unknown TTO							

[a] Incidence rate (IR) Source: Willame et al 2021. Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project. Drug Safety (2021) 44:383–395
Exposure until 28 December 2021
BCC, Brighton Criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown.

Observed versus expected analyses stratified by age and gender in the United Kingdom, using UK incidence rates from Willame et al 2021 [B], ie, UK The Health Improvement Network (UK_THIN), are presented in Table 112. The observed numbers are presented both including and excluding cases with an unknown time to onset.

Table 112 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 15-24 years UK THIN	42	1.2	661657	1	0.91	1.1 (0.03 - 6.12)	Observed > expected
Female 25-44 years UK THIN	42	2.6	7748245	17	23.17	0.73 (0.43 - 1.17)	Observed < expected
Female 45-64 years UK THIN	42	1.9	9050095	14	19.77	0.71 (0.39 – 1.19)	Observed < expected
Female 65 years+ UK THIN	42	0.8	7411952	7	6.82	1.03 (0.41 - 2.11)	Observed > expected
Female Overall	42	1.6	24872206	45	45.76	0.98	Observed < expected

Table 112 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
UK THIN						(0.72 - 1.32)	
Female 15-24 years UKTHIN +Unk TTO	42	1.2	661657	2	0.91	2.2 (0.27 - 7.94)	Observed > expected
Female 25-44 years UKTHIN +Unk TTO	42	2.6	7748245	23	23.17	0.99 (0.63 - 1.49)	Observed < expected
Female 45-64 years UKTHIN +Unk TTO	42	1.9	9050095	25	19.77	1.26 (0.82 - 1.87)	Observed > expected
Female 65 years+ UKTHIN +Unk TTO	42	0.8	7411952	8	6.82	1.17 (0.51 - 2.31)	Observed > expected
Female Overall UKTHIN +Unk TTO	42	1.6	24872206	66	45.76	1.44 (1.12 - 1.83)	Observed significantly > expected
Male 15-24 years UK THIN	42	0.7	490479	2	0.39	5.13 (0.62 – 18.52)	Observed > expected
Male	42	1.5	7299631	7	12.59	0.56	Observed < expected

Table 112 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years UK THIN						(0.22 - 1.15)	
Male 45-64 years UK THIN	42	1.4	9841345	15	15.84	0.95 (0.53 - 1.56)	Observed < expected
Male 65 years + UK THIN	42	0.9	6348392	7	6.57	1.07 (0.43 - 2.2)	Observed > expected
Male Overall UK THIN	42	1.1	23980140	36	30.33	1.19 (0.83 - 1.64)	Observed > expected
Male 15-24 years UKTHIN +Unk TTO	42	0.7	490479	2	0.39	5.13 (0.62 - 18.52)	Observed > expected
Male 25-44 years UKTHIN +Unk TTO	42	1.5	7299631	8	12.59	0.64 (0.27 – 1.25)	Observed < expected
Male 45-64 years UKTHIN +Unk TTO	42	1.4	9841345	25	15.84	1.58 (1.02 - 2.33)	Observed significantly > expected
Male 65 years +	42	0.9	6348392	11	6.57	1.67 (0.84 - 3)	Observed > expected

Table 112 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
UKTHIN +Unk TTO							
Male Overall UKTHIN +Unk TTO	42	1.1	23980140	55	30.33	1.81 (1.37 - 2.36)	Observed significantly > expected

[a] Incidence Rate (IR) Source at Willame et al 2021 [B] Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project. Drug Safety (2021) 44:383–395

CI, Confidence Interval; E, Expected; O, Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom

An observed versus expected analysis, including cases fulfilling Brighton collaboration levels 1-3, stratified by age and gender in the UK are provided below, using background rates from UK THIN are presented in Table 113.

Table 113 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 15-24 years UK THIN BCC 1-3	42	1.2	661657	0	0.91	0 (0 - 4.05)	Observed < expected
Female 25-44 years UK THIN BCC 1-3	42	2.6	7748245	6	23.17	0.26 (0.1 - 0.56)	Observed significantly < expected

Table 113 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 45-64 years UK THIN BCC 1-3	42	1.9	9050095	2	19.77	0.1 (0.01 - 0.37)	Observed significantly < expected
Female 65 years+ UK THIN BCC 1-3	42	0.8	7411952	0	6.82	0 (0 - 0.54)	Observed significantly < expected
Female Overall UK THIN BC 1-3	42	1.6	24872206	8	45.76	0.17 (0.08 - 0.34)	Observed significantly < expected
Female 15-24 years UKTHIN +Unk TTO BCC 1-3	42	1.2	661657	0	0.91	0 (0 - 4.05)	Observed < expected
Female 25-44 years UKTHIN +Unk TTO BCC 1-3	42	2.6	7748245	8	23.17	0.35 (0.15 - 0.68)	Observed significantly < expected

Table 113 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 45-64 years UKTHIN +Unk TTO BCC 1-3	42	PPD					Observed significantly < expected
Female 65 years + UKTHIN +Unk TTO BCC 1-3	42						Observed significantly < expected
Female Overall UKTHIN +Unk TTO BCC 1-3	42	1.6	24872206	14	45.76	0.31 (0.17 - 0.51)	Observed significantly < expected
Male 15-24 years UK THIN BCC 1-3	42	0.7	490479	0	0.39	0 (0 - 9.46)	Observed < expected
Male 25-44 years UK THIN	42	1.5	7299631	0	12.59	0 (0 - 0.29)	Observed significantly < expected

Table 113 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
BCC 1-3							
Male 45-64 years UK THIN BCC 1-3	42	1.4	9841345	7	15.84	0.44 (0.18 - 0.91)	Observed significantly < expected
Male 65 **years +** UK THIN BCC 1-3	42	0.9	6348392	1	6.57	0.15 (0 - 0.85)	Observed significantly < expected
Male Overall UK THIN BCC 1-3	42	1.1	23980140	8	30.33	0.26 (0.11 - 0.52)	Observed significantly < expected
Male 15-24 years UKTHIN +Unk TTO BCC 1-3	42	0.7	490479	0	0.39	0 (0 - 9.46)	Observed < expected
Male 25-44 years UKTHIN +Unk TTO	42	1.5	7299631	0	12.59	0 (0 - 0.29)	Observed significantly < expected

Table 113 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/ Gender	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
BCC 1-3							
Male 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.4	9841345	8	15.84	0.51 (0.22 - 1)	Observed significantly < expected
Male 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.9	6348392	1	6.57	0.15 (0 – 0.85)	Observed significantly < expected
Male Overall UKTHIN +Unk TTO BCC 1-3	42	1.1	23980140	9	30.33	0.3 (0.14 - 0.56)	Observed significantly < expected

[a] Incidence Rate (IR) Source at Willame et al 2021 [B] Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project. Drug Safety (2021) 44:383–395

BCC, Brighton collaboration criteria; CI, Confidence Interval; E Expected; O Observed; TTO, Time to Onset; UK United Kingdom; Unk, Unknown

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the United Kingdom, using UK incidence rates from Willame et al 2021 [B] ie, UK The Health Improvement Network (UK_THIN), are presented in. Table 114.

Table 114 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 15-24 years/ Dose 1	42	0.7	251355	0	0.2	0 (0 - 18.44)	Observed < expected
Male/ 25-44 years/ Dose 1	42	1.5	2313716	6	3.99	1.5 (0.55 – 3.27)	Observed > expected
Male/ 45- 64 years/ Dose 1	42	1.4	6363015	12	10.24	1.17 (0.61 - 2.05)	Observed > expected
Male/ 65 yrs +/ Dose 1	42	0.9	3198768	3	3.31	0.91 (0.19 - 2.65)	Observed < expected
Male/ Overall/ Dose 1	42	1.1	12127070	26	15.34	1.69 (1.11 - 2.48)	Observed significantly > expected
Male/ 15-24 years/ Dose 1/ BCC 1-3	42	0.7	251355	0	0.2	0 (0 - 18.44)	Observed < expected
Male/ 25-44 years/ Dose 1/ BCC1-3	42	1.5	2313716	0	3.99	0 (0 - 0.92)	Observed significantly < expected
Male/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.4	6363015	6	10.24	0.59 (0.22 - 1.28)	Observed < expected
Male/ 65 yrs +/ Dose 1/ BCC 1-3	42	0.9	3198768	0	3.31	0 (0 - 1.11)	Observed < expected

Table 114 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ Overall/ Dose 1/ BCC-1-3	42	1.1	12127070	6	15.34	0.39 (0.14 - 0.85)	Observed significantly < expected
Male/ 15-24 years/ Dose 2	42	0.7	238794	0	0.19	0 (0 - 19.42)	Observed < expected
Male/ 25-44 years/ Dose 2	42	1.5	2223134	0	3.83	0 (0 - 0.96)	Observed significantly < expected
Male/ 45- 64 years/ Dose 2	42	1.4	6233036	2	10.03	0.2 (0.02 – 0.72)	Observed significantly < expected
Male/ 65 yrs +/ Dose 2	42	0.9	3141956	2	3.25	0.62 (0.07 - 2.22)	Observed < expected
Male/ Overall/ Dose 2	42	1.1	11836997	4	14.97	0.27 (0.07 - 0.68)	Observed significantly < expected
Male/ 15-24 years/ Dose 2/ BCC 1-3	42	0.7	238794	0	0.19	0 (0 - 19.42)	Observed < expected
Male/ 25-44 years/ Dose 2/ BCC 1-3	42	1.5	2223134	0	3.83	0 (0 - 0.96)	Observed significantly < expected
Male/ 45- 64 years/ Dose 2/ BCC 1-3	42	1.4	6233036	0	10.03	0 (0 - 0.37)	Observed significantly < expected

Table 114 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 65 yrs +/ Dose 2/ BCC 1-3	42	0.9	3141956	1	3.25	0.31 (0.01 – 1.71)	Observed < expected
Male/ Overall/ Dose 2/ BCC 1-3	42	1.1	11836997	1	14.97	0.07 (0 - 0.37)	Observed significantly < expected
Female/ 15-24 years/ Dose 1	42	1.2	338264	1	0.47	2.13 (0.05 - 11.85)	Observed > expected
Female/ 25-44 years/ Dose 1	42	2.6	2624476	12	7.85	1.53 (0.79 - 2.67)	Observed > expected
Female/ 45- 64 years/ Dose 1	42	1.9	5868905	9	12.82	0.7 (0.32 - 1.33)	Observed < expected
Female/ 65 yrs +/ Dose 1	42	0.8	3733451	4	3.43	1.17 (0.32 - 2.99)	Observed > expected
Female/ Overall/ Dose 1	42	1.6	12565284	30	23.12	1.3 (0.88 - 1.85)	Observed > expected
Female/ 15-24 years/ Dose 1/ BCC 1-3	42	1.2	338264	0	0.47	0 (0 - 7.85)	Observed < expected
Female/ 25-44 years/ Dose 1/ BCC 1-3	42	2.6	2624476	3	7.85	0.38 (0.08 - 1.12)	Observed < expected

Table 114 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.9	5868905	1	12.82	0.08 (0 – 0.43)	Observed significantly < expected
Female/ 65 yrs +/ Dose 1/ BCC 1-3	42	0.8	3733451	0	3.43	0 (0 - 1.08)	Observed < expected
Female/ Overall/ Dose 1/ BCC 1-3	42	1.6	12565284	4	23.12	0.17 (0.05 - 0.44)	Observed significantly < expected
Female/ 15-24 years/ Dose 2	42	1.2	322959	0	0.45	0 (0 - 8.2)	Observed < expected
Female/ 25-44 years/ Dose 2	42	2.6	2528039	2	7.56	0.26 (0.03 - 0.96)	Observed significantly < expected
Female/ 45- 64 years/ Dose 2	42	1.9	5760637	3	12.59	0.24 (0.05 - 0.7)	Observed significantly < expected
Female/ 65 yrs +/ Dose 2	42	0.8	3662563	0	3.37	0 (0 - 1.09)	Observed < expected
Female/ Overall/ Dose 2	42	1.6	12274265	6	22.58	0.27 (0.1 - 0.58)	Observed significantly < expected
Female/ 15-24 years/ Dose 2/ BCC 1-3	42	1.2	322959	0	0.45	0 (0 – 8.2)	Observed < expected

Table 114 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 25-44 years/ Dose 2 / BCC 1-3	42	2.6	2528039	1	7.56	0.13 (0 - 0.74)	Observed significantly < expected
Female/ 45- 64 years/ Dose 2 / BCC 1-3	42	1.9	5760637	0	12.59	0 (0 - 0.29)	Observed significantly < expected
Female/ 65 yrs +/ Dose 2 / BCC 1-3	42	0.8	3662563	0	3.37	0 (0 - 1.09)	Observed < expected
Female/ Overall/ Dose 2 / BCC 1-3	42	1.6	12274265	1	22.58	0.04 (0 - 0.25)	Observed significantly < expected

[a] Incidence Rate (IR) Source at Willame et al 2021 [B] Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project. Drug Safety (2021) 44:383-395

BCC, Brighton collaboration criteria, CI, Confidence Interval, E Expected, O Observed, TTO: Time to onset; UK United Kingdom, Unk, Unknown, yrs Years.

Observed versus expected analyses stratified by dose number, age and gender, BCC in the EEA/ UK are presented in Table 115.

Table 115 Observed versus expected analysis, stratified by Dose, age, BCC in the EEA/UK

Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
15-24 years/ Dose 1	42	0.64	1183977	2	0.87	2.3 (0.28 - 8.3)	Observed > expected

Table 115 Observed versus expected analysis, stratified by Dose, age, BCC in the EEA/UK

Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years/ Dose 1	42	1.36	10619906	27	16.61	1.63 (1.07 - 2.37)	Observed significantly > expected
45- 64 years/ Dose 1	42	1.23	15638894	31	22.12	1.4 (0.95 - 1.99)	Observed > expected
65 yrs +/ Dose 1	42	0.76	21176930	15	18.51	0.81 (0.45 - 1.34)	Observed < expected
Overall/ Dose 1	42	0.97	90124332	85	100.53	0.85 (0.68 - 1.05)	Observed < expected
15-24 years/ Dose 1/ BCC 1-3	42	0.64	1183977	0	0.87	0 (0 - 4.24)	Observed < expected
25-44 years/ Dose 1/ BCC1-3	42	1.36	10619906	5	16.61	0.3 (0.1 - 0.7)	Observed significantly < expected
45- 64 years/ Dose 1/ BCC 1-3	42	1.23	15638894	8	22.12	0.36 (0.16 - 0.71)	Observed significantly < expected
65 yrs +/ Dose 1/ BCC 1-3	42	0.76	21176930	0	18.51	0 (0 - 0.2)	Observed significantly < expected
Overall/ Dose 1/ BCC-1-3	42	0.97	90124332	13	100.53	0.13 (0.07 - 0.22)	Observed significantly < expected
15-24 years/ Dose 2	42	0.64	1017525	0	0.75	0 (0 - 4.92)	Observed < expected
25-44 years/ Dose 2	42	1.36	9532871	2	14.91	0.13 (0.02 - 0.48)	Observed significantly < expected

Table 115 Observed versus expected analysis, stratified by Dose, age, BCC in the EEA/UK

Age group / Dose #	Risk window	Background rates[a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
45- 64 years/ Dose 2	42	1.23	14861461	7	21.02	0.33 (0.13 - 0.69)	Observed significantly < expected
65 yrs +/ Dose 2	42	0.76	20343832	4	17.78	0.22 (0.06 - 0.58)	Observed significantly < expected
Overall/ Dose 2	42	0.97	77554203	14	86.51	0.16 (0.09 - 0.27)	Observed significantly < expected
15-24 years/ Dose 2/ BCC 1-3	42	0.64	1017525	0	0.75	0 (0 - 4.92)	Observed < expected
25-44 years/ Dose 2/ BCC 1-3	42	1.36	9532871	1	14.91	0.07 (0 - 0.37)	Observed significantly < expected
45- 64 years/ Dose 2/ BCC 1-3	42	1.23	14861461	0	21.02	0 (0 - 0.18)	Observed significantly < expected
65 yrs +/ Dose 2/ BCC 1-3	42	0.76	20343832	1	17.78	0.06 (0 - 0.31)	Observed significantly < expected
Overall/ Dose 2/ BCC 1-3	42	0.97	77554203	2	86.51	0.02 (0 - 0.08)	Observed significantly < expected

[a] Incidence Rate (IR) Source at Willame et al 2021 [B] Incidence rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project. Drug Safety (2021) 44:383-395

BCC, Brighton collaboration classification criteria; CI, Confidence Interval; E Expected; EEA, European Economic Area O Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom, yrs Years.

Observed vs expected analysis summary:

When the observed versus expected analysis is carried out overall for global reports for all ages and genders, observed cases are significantly less than expected for all stratifications provided.

When stratified by age only in the EEA and the UK using the ADVANCE EUROPE rates, observed cases are significantly more than expected for age groups 15-24 years and 45-64 years, regardless of whether cases with an unknown time to onset are included or not. For the age group 25-44 years, observed cases are more than expected, however the disproportionality was not significant when cases with unknown TTO are not included. For the older age group (65+ years), observed cases are significantly less than expected, when cases with an unknown TTO are not included. When the cases with an unknown TTO are included for the same age group (65+ years), observed cases are less than expected, without a significant disproportionality.

When only cases of transverse myelitis fulfilling BCC levels 1-3 are included, observed cases are significantly less than/less than expected for all stratifications, apart from the youngest age group where observed cases are more than expected (2 cases vs 1.62) without the result being significant.

The observed cases for females in the UK using the rate from UKTHIN are either more or less than expected. When stratified by age and gender, observed cases for females were greater than expected in the age group 15- 24 years and 65+ years, without the result being significant. Observed cases for female overall was significantly more than expected when rate from UKTHIN, when cases with unknown TTO were included. For other stratifications, observed cases were either more or less than expected without the result being significant.

When only cases fulfilling BCC levels 1-3 are included, observed cases are either less or significantly less than expected for all age stratifications (result is not significant for the youngest age group, 15-24 years, however, there are no observed cases with BCC 1-3 in that age group).

When stratified by age and gender, the observed cases for males are significantly more than expected for males overall when cases with an unknown TTO are included. For all age stratifications in males, the numbers are low, leading to the finding that the results for each age group are not significant. When the UKTHIN rates are used, the youngest age group (15-24 years) and the oldest age group (65+ years) have observed cases more than expected. When cases with unknown TTO were included, however, all age groups had observed higher than expected, the only exception being the age group 25-44 years.

When males are stratified by BCC levels 1-3, observed cases were less than expected in all age groups.

Cases were also stratified by dose. For Dose 1 Overall, the observed cases were less than expected. When Dose 1 cases in males were stratified using UK THIN background rates, the cases were either more or less than expected. Overall the observed number of cases was significantly more than expected (26 cases to 15.34). Cases fulfilling BCC 1-3 criteria (overall and ages 25-44 years), where observed cases were significantly less than expected. Cases in female patients after

dose 1 stratified using the same UK THIN background rates did not have any significant findings except the BCC 1-3 cases where the observed cases were significantly lesser than expected (overall and ages 45-64 years). When stratified by age only in the EEA and the UK using the ADVANCE EUROPE rates, the observed cases were more than expected in all age groups except the 65+ years range where it was less than expected for the first dose. When stratified by cases fulfilling BCC 1-3, observed cases were significantly lesser than expected.

For Dose 2, overall, the observed cases were significantly less than expected with and without unknown TTO cases and BCC 1-3. With the UK THIN background rates, observed cases were mostly significantly less than expected in males and females after dose 2. This was also significantly less than observed for cases stratified by dose, age and BCC in the EEA/ UK.

Literature

A cumulative literature review through 28 December 2021 was conducted to review the occurrence of TM is association with COVID-19 VACCINE ASTRAZENECA using the key terms COVID-19 vaccines and Vaxzevria, transverse myelitis. The searches were conducted in the Embase and InsightMeme. The searches revealed 37 results. Relevant articles from the search are discussed and presented in the literature review for TM here below.

Transverse myelitis is an acute inflammatory condition in a limited area of the spinal cord. The inflammation typically occurs acutely - within a few hours, or sub acutely, a little more slowly with gradual development over 1-2 weeks. The inflammation usually quickly leads to the development of paralysis and weakened sensation in the skin below the injury, and to disturbance of intestinal and / or bladder function. Transverse myelitis is rare. The condition can be the result of another disease, but the form in which one has transverse myelitis without a known cause occurs in approx. 1-4 people per 1 million inhabitants. In some known diseases, transverse myelitis can occur as part of the disease - this includes Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD) (Helseinformatikk 2020). TM has been associated with certain viral illnesses. More rarely, it has been seen following certain vaccinations.

Roman et al 2021describes a comprehensive clinical review of 43 patients with COVID-19-associated ATM, from 21 countries published from March 2020 to January 2021. In addition, several articles report cases of Longitudinal extensive transverse myelitis (LETM), TM or ATM following AstraZeneca COVID-19 vaccination (Pagenkopf et al 2021, Choi et al 2021, Singh Malhotra et al 2021, Vegezzi et al 2021, Tan et al 2021, Notghi et al 2021, Camera et al 2021)

A series of articles do report TM as an adverse event to other COVID-19 vaccines, with the overall conclusion that there is currently insufficient data to form a direct association between the COVID-19 vaccine and transverse myelitis (Alshararni 2021, Banks et al 2021, Erdem et al 2021, Ersoy 2021, Gao et al 2021, Tijmes et al 2021, Xu et al 2021, Sepahvand et al 2021)

Since coronavirus disease-2019 (COVID-19) outbreak in January 2020, several pieces of evidence suggested an association between this rare neurological syndrome in association with SARS-CoV-

2 infection itself. Most findings were reported in the form of case reports or case series, whereas a comprehensive overview is still lacking (Bonifacio et al 2021).

Thus far, the review of available literature did not identify any definitive evidence of causal association between Transverse myelitis and COVID-19 VACCINE AstraZeneca.

Overall Summary

Based on a review of currently available information (clinical, post-market and literature), it is considered that a reasonable possibility of a causal relationship between COVID-19 VACCINE ASTRAZENECA and Transverse myelitis cannot be established at this time. The pathogenesis TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown. In summary, COVID-19 VACCINE ASTRAZENECA viral vector proteins presented non-significant molecular identity to human CNS proteins that could theoretically induce TM.

There were 23 cases of TM (fulfilling at least BC 3 criteria) assessed to be classified as Possible according to WHO-UMC causality criteria. However, for 7 of the 23 cases the Possible classification was based solely on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc). For the remaining 16 cases the event could also be explained by the vaccinees' diseases or other medications.

In addition, an observed versus expected analysis of cases meeting Brighton collaboration criteria levels 1-3 showed that the observed number of TM cases fulfilling case definition are less than number of expected cases in all risk windows.

Furthermore, the current COVID-19 VACCINE ASTRAZENECA CDS Version 10 (dated 02 November 2021), contains the following text in Section 4.4.

"Very rare events of demyelinating disorders have been reported following vaccination with Vaxzevria. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with Vaxzevria should be considered."

Transverse myelitis is being studied in "A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns" (D8111R00006). This is a multi-country secondary data use study which utilises data from the Clinical Practice Research Datalink (CPRD) in the UK, the Valencia Integrated Database (VID) and the SIDIAP database in Spain, the Agenzia Regionale di Sanità Toscana (ARS Toscana) in Italy, and PHARMO Database Network in the Netherlands.

In addition to a retrospective cohort design, the study uses a self-controlled risk interval (SCRI) design. In SCRI design, the Incidence rate ratio comparing the rate of an event in a period hypothesised to be at increased risk due to exposure ("risk period" or "exposed person-time") will be compared with a prespecified postvaccination period within the same individual that falls after

the risk period ("control period" or "unexposed person-time"). This is very similar to SCCS, the main difference being that the control period comes after the risk period.

The results of the SCRI analysis will be available with the final study report, expected October 2023. Three interim reports (expected April and October 2022 and April 2023) will focus on intermediate results of the cohort analysis.

Conclusion

In conclusion, it is AstraZeneca's opinion that no changes to the COVID-19 VACCINE ASTRAZENECA CDS, RMPs, corresponding local labels or product leaflets are warranted based on the review of currently available information.

Surveillance of Transverse Myelitis will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the AESI of Nervous system disorders, including immune-mediated neurological conditions.

16.3.1.2 Vaccine-Associated Enhanced Disease (VAED) / Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Review of Cases

Cumulative data through 28 December 2021

A cumulative search of the AstraZeneca Global Patient Safety Database (data cut-off: 28 December 2021) was conducted on 29 December 2021 for adverse event reports of Vaccine-associated enhanced disease (VAED)/ Vaccine-associated enhanced respiratory disease (VAERD) in association with the use of AZD1222. There have been 1739 case reports of potential VAED/ VAERD which included 1811 events. These events include Pneumonia (760), Coagulopathy (342), COVID-19 pneumonia (266), Respiratory failure (149), Pneumonitis (87), Multiple organ dysfunction syndrome (80), Acute respiratory failure (59), Pulmonary haemorrhage (26), Cytokine storm (9), Organ failure (9), Mechanical ventilation (5), Vaccine associated enhanced disease (5), Acute lung injury (3), Autoimmune myositis (3), Cytokine release syndrome (3), Immune-mediated myositis (3), Cytokine increased (1), SARS-CoV-2 sepsis (1).

Among these 1739 cases, majority were from spontaneous source (1,697, 97.6%), followed by non-interventional studies (20, 1.2%), then literature (19, 1.1%) and AZ-sponsored clinical trials (3, 0.2%). Of these 1739 cases, 862 cases were reported from females and 839 from males. Among total cases, 751 (1,524 serious and 215 non serious) were medically confirmed cases with the use of COVID-19 Vaccine AstraZeneca. There were 674 (39%) case reports from elderly (≥65 years of age) vaccinees, 926 (53%) from adult (18 - 64 years of age) vaccinees, 02 from pediatric vaccinees and age was unknown in 137 (8%) vaccinees. In 312 of the 1739 cases, the outcome of events was reported as fatal.

Interval Period (29 June 2021 – 28 December 2021)

During the interval period (29 June 2021 to 28 December 2021) covered by this report 1008 events from 967 cases were retrieved under this AESI concept, which include Pneumonia (381), COVID-19 pneumonia (194), Coagulopathy (174), Respiratory failure (83), Pneumonitis (50), Multiple organ dysfunction syndrome (47), Acute respiratory failure (39), Pulmonary Haemorrhage (15), Organ failure (5), Mechanical ventilation (4), Autoimmune myositis (3), Cytokine storm (3), Immune-mediated myositis (3), Vaccine associated enhanced disease (3), Acute lung injury (2), Cytokine release syndrome (1), and SARS-CoV-2 sepsis (1).

Among these 967 cases, majority were from spontaneous source (941, 97.3%), followed by non-interventional studies (13, 1.3%), then literature (11, 1.1%) and AZ-sponsored clinical trials (2, 0.2%). Of these 967 cases, 450 (438 serious and 12 non serious) were medically confirmed cases with the use of COVID-19 Vaccine AstraZeneca. There were 391 case reports from elderly vaccinees, 510 from adult vaccinees, 02 from paediatric vaccinees and age was unknown in 64 vaccinees. In 174 of the 967 cases, the outcome of potential VAED/VAERD events was fatal.

There were 155 potential VAED/VAERD cases that tested positive for COVID-19 postvaccination (range 1-305 days post-vaccination; unknown for 54 cases). Of these 155 cases, 30 were reported after the first dose and 103 after the second dose. Of the 30 cases after the first dose, and the outcome was fatal in 07 cases (05 elderly and 02 adult vaccinees). The causes of death in all these 07 fatal cases after the first dose were COVID-19 pneumonia (06), Pneumonia (01), Atrial fibrillation (01), Rheumatoid arthritis (01), Severe acute respiratory syndrome (01), Chronic kidney disease (01), Bronchial hyperreactivity (01), Type 2 diabetes mellitus (01), Cardio-respiratory distress (01) and Sepsis (01).

Of the 103 cases after the second dose, fatal outcome was reported in 07 cases (05 elderly and 02 adult vaccinees). The causes of death in all these 07 fatal cases after the second dose were Respiratory failure (04), Vaccination failure (04), COVID-19 pneumonia (03), COVID-19 (03), Intestinal ischaemia (01), and Vaccine associated enhanced disease (01).

Literature

Agrawal et al 2021 presented results from a prospective cohort study using the national surveillance platform, in Scotland. The objective was to estimate the frequency of COVID-19 admissions to hospital or deaths 14 days or more after receiving the first vaccine dose [BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) COVID-19 vaccines] and to characterise individuals with these outcomes in terms of demographic and clinical considerations. The national surveillance comprised vaccination, primary care, RT-PCR testing, hospitalisation, and mortality records for 5·4 million people (around 99% of the population).

Individuals were followed up from receiving their first dose of COVID-19 vaccines until admission to hospital for COVID-19, death, or the end of the study period on 18 April 2021.

Results

A total of 2,572,008 individuals received the first dose of vaccine [841,090 (32·7%) received BNT162b2 and 1,730,918 (67·3%) received ChAdOx1] out of which 1196 (<0·1%, 4·6 events per

1000 person-years) individuals were admitted to hospital or died due to COVID-19 illness (883 hospitalised, of whom 228 died, and 313 who died due to COVID-19 without hospitalisation) 14 days or more after their first vaccine dose. Over the same period, the rate of hospitalisation or death from COVID-19 was 8·57 events per 1000 person-years (10,282 events in total) in the unvaccinated population in Scotland, despite the fact that this unvaccinated group was a much younger population. These severe COVID-19 outcomes were associated with older age (≥80 years vs 18–64 years adjusted RR 4·75, 95% CI 3·85–5·87), comorbidities (five or more risk groups vs less than five risk groups 4·24, 3·34–5·39), hospitalisation in the previous 4 weeks (3·00, 2·47–3·65), high-risk occupations (ten or more previous COVID-19 tests vs less than ten previous COVID-19 tests 2·14, 1·62–2·81), care home residence (1·63, 1·32–2·02), socioeconomic deprivation (most deprived quintile vs least deprived quintile 1·57, 1·30–1·90), being male (1·27, 1·13–1·43), and being an ex-smoker (ex-smoker vs non-smoker 1·18, 1·01–1·38). A history of COVID-19 before vaccination was protective (0·40, 0·29–0·54). This analysis was performed during a period where there was a high background incidence of SARS-CoV-2 infection and a national lockdown in place in Scotland.

Conclusions

The authors found a small risk of hospitalisation or death due to COVID-19 illness 14 days or more days after the first vaccine dose, with older people, those with greater numbers of long-term conditions, people admitted to hospital in the recent weeks before their vaccination, people in high-risk occupations, care home residents, those from deprived backgrounds, men, and ex-smokers at the highest risk. By contrast, previous infection with COVID-19 was associated with a reduced risk of these events following vaccination. Overall, the rate of severe COVID-19 outcomes for individuals from 14 days onwards after a first dose of ChAdOx1 or BNT162b2 was very low, with less than 0·05% of people who received at least one vaccine suffering an adverse breakthrough event.

AstraZeneca comment: *This article is a large prospective cohort real world study but without a matched comparison cohort. During a period of high background incidence of SARS-CoV-2 infection in Scotland with rate of hospitalisation or death from COVID-19 being 8·57 events per 1000 person-years, the rate of severe COVID-19 outcomes for individuals from 14 days onwards after an incomplete schedule of ChAdOx1 or BNT162b2 was very low (less than 0·05%, 4·6 events per 1000 person-years) which does not support a causal relationship to Covid-19 vaccination.*

However, there was no information on number/frequency of all COVID-19 positive cases (irrespective of symptoms or severity) post COVD-19 vaccination. Also, the time to onset of COVID-19 was not reported and therefore the co-existence of COVID-19 pre-vaccination or in the reactogenic period could not be confirmed. As per CDC 2021 *guidance, the incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset with on study reporting onset of symptoms within 11.5 days of infection for 97.5% of people with COVID-19. Interestingly however, the comparative frequency of hospitalization or death due to COVID-19 in prospective time period compared to 14-20 day period in either both or individual vaccines showed a decreasing trend which was also statistically significant [21–27 days - 0·66 (0·56–0·78); 28–34 days - 0·48 (0·40–0·57); 35–41 days - 0·37 (0·30–0·45); 42–128*

days - 0·23 (0·20–0·27)]. This trend could possibly be attributed to vaccine efficacy. Moreover, a decrease was seen in the event rate following second dose of vaccination as compared to first dose of vaccination (0·9 vs 4.6 per 1000 person-years) for hospitalization or death due to COVID-19 which could again possibly be attributed to vaccine efficacy.

On sub-group analysis of risk factors, an increasing trend in hospitalization or death due to COVID-19 was seen with increased strata of concurrent risk groups 1 risk group - 1·39 (1·13–1·71); 2 risk groups - 2·40 (1·95–2·95); 3 risk groups - 3·18 (2·55–3·95); 4 risk groups - 2·90 (2·26–3·73); ≥5 risk groups - 4·24 (3·34–5·39)]. The risk groups comprised Cancer (such as blood cancer), Cerebrovascular disease (such as stroke), Chronic lung disease (such as COPD, pulmonary hypertension, pulmonary embolus), Diabetes mellitus type 1 and type 2, Heart conditions (such as heart failure), severe mental illness and so on and which have been identified as underlying medical conditions associated with higher risk for severe COVID-19 supported by at least one meta-analysis or systematic review in the backdrop of skewness towards elderly age (especially >80 years) (Kompaniyets et al 2021).

In summary, due to lack of matched comparison group, incomplete vaccine schedule, no information on SARS-CoV-2 serotype, COVID-19 onset and frequency of COVID-19 positivity and study design precluding causality determination, thus a comprehensive causal assessment of vaccine to severe COVID-19 outcomes was not possible. However, the decreasing trends for hospitalization or death following vaccination does not support a causal association.

Mechanism of action

The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from nonclinical studies (Haynes et al 2020). VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD may be specific to the lower respiratory tract or may be part of a systemic process.

Summary

On review of 967 cases of VAED/VAERD received during the reporting period, majority (89%) of them were reported as serious, 18% cases reported fatal outcome and around 53% were reported from adult age group. Notably, 155 (16%) of potential VAED/VAERD cases received during the reporting period tested positive for COVID-19 postvaccination of which 30 cases occurred after the first dose and 103 cases occurred after the second dose of COVID-19 VACCINE ASTRAZENECA. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, storage and transport conditions of the vaccine, which precluded a proper causal assessment. As of yet, no mechanism of action has been identified. No new safety information on this topic was identified through the review of literature.

From the data identified during the reporting period and also taking into account the cumulative experience, no causal relationship between VAED/VAERD and COVID-19 VACCINE ASTRAZENECA could be established.

Conclusion

In conclusion, it is AstraZeneca's opinion that no changes to the COVID-19 VACCINE ASTRAZENECA CDS, RMPs, corresponding local labels or product leaflets are warranted based on the review of currently available information.

The topic of VAED with COVID-19 VACCINE ASTRAZENECA will continue to be closely monitored by AstraZeneca.

More detailed information regarding this important potential risk is provided in Section 16.4.2.

16.3.1.3 CVST without thrombocytopenia

Pre-Clinical Data

There was no pre-clinical data on CVST from AstraZeneca safety studies with AZD1222. There were no pathology findings. An animal model of spontaneously occurring CVST does not exist. Also, there are no animal strains which are CVST-prone.

Review of Cases: Post-authorisation data

Cumulative Review through 28 December 2021

A cumulative search of the AstraZeneca global safety database was conducted through 28 December 2021 using the following MedDRA (v24.1) HLT: Cerebrovascular venous and sinus thrombosis (CVST). To identify the cases of CVST without co-reported thrombocytopenia, the following were excluded from the search results described above: any cases with events from the HLT: Thrombocytopenia, SMQ: Hematopoietic thrombocytopenia (Narrow), or cases with platelet values less than 150,000 per microliter.

After applying the exclusion criteria, 508 cases with CVST without thrombocytopenia were received from vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 508 case reports, 1 case was from the clinical trial, 21 literature cases, 3 cases from non-interventional/post-marketing and 483 cases are from spontaneous sources.

The reported CVST PTs from the 508 cases were: Cerebral venous sinus thrombosis (322), Cerebral venous thrombosis (133), Superior sagittal sinus thrombosis (27), Transverse sinus thrombosis (30) and Cavernous sinus thrombosis (16).

Of the 508 case reports, 501 were reported as serious and 7 were reported as non-serious; 317 were medically confirmed. The seriousness criteria for the 501 serious cases of CVST without thrombocytopenia included: death (37), life-threatening (114), hospitalization or prolongation of existing hospitalization (320), Congenital anomaly (1), persistent or significant disability or

incapacity (36) and medically significant (273). A single case may have met more than one criteria for serious.

Approximately one third of the cases 166 (33%) were reported from Germany and 148 (29%) cases were reported from UK. A total of 307 (60%) case reports were reported in females, 181 (36%) were reported in males, and in 20 (4%) the gender was not reported. The median age was 51 years with a range of 18 to 98 years. Out of 508 reported cases, 346 (68%) occurred in adults (18-64 years of age), 112 (22%) in elderly (≥ 65 years of age), and in 50 (10%) the age was not reported.

Of the 508 case reports, 37 (7.1%) cases had a reported fatal outcome. There were 21 medically confirmed cases and 16 non-medically confirmed cases with a fatal outcome. Of the 37 fatal cases, 21 (56.7%) occurred in the age group of 18-49. Age/gender and percentage of the total cases for the fatal reports are presented in Table 116.

Table 116 CVST Without Thrombocytopenia Case Reports by age/gender, and fatality

Age group	Female N (Fatal cases) Fatal%	Male N (Fatal cases) Fatal%	Gender Unknown N (Fatal cases) Fatal%	Total N (Fatal cases) Fatal%
Age - 18-29 Years	57 (2) 3.5 %	14 (4) 28.6%	0 (0) 0%	71 (6) 8.5%
Age - 30-39 Years	46 (3) 6.5%	11 (3) 27.3%	0 (0) 0%	57 (6) 10.5%
Age - 40-49 Years	62 (6) 9.7%	22 (3) 13.6%	0 (0) 0%	84 (9) 10.7%
Age - 50-59 Years	48 (2) 4.2%	43 (1) 2.3%	1 (1) 100%	92 (4) 4.4%
Age - 60-69 Years	38 (2) 5.3%	49 (5) 10.2%	0 (0) 0%	87 (7) 8.1%
Age - 70-79 Years	27 (1) 3.7%	26 (1) 3.9%	0 (0) 0%	53 (2) 3.8%
Age - 80+ Years	10 (1) 10%	3 (0) 0%	0 (0) 0%	13 (1) 7.7%
Age Unknown	19 (1) 5.3%	13 (0) 0%	19 (1) 5.3%	51 (2) 3.9%
Grand Total	**307 (18) 5.9 %**	**181 (17) 9.4%**	**20 (2) 10%**	**508 (37) 7.3%**

CVST Cerebral Venous Sinus Thrombosis, N, Number of cases.

The reported PTs with a fatal outcome in the 37 cases of CVST without thrombocytopenia in order of frequency were Cerebral venous thrombosis (17), Cerebral venous sinus thrombosis (15), Cavernous sinus thrombosis (5) and transverse sinus thrombosis (1). Twenty-One fatal cases occurred in the age group of 18-49 years (56% of the case reports of all age groups). Out of 21 fatal cases 11 cases occurred in the females and 10 fatal cases occurred in males in the age group of 18-49. The most common reported PTs with a fatal outcome in 18 to 49 age group was: Cerebral venous sinus thrombosis (10) and Cerebral venous thrombosis (10).

Reported outcomes in the remaining 472 non-fatal case reports of CVST without thrombocytopenia were: Not Recovered 194 (38.2%), Recovered 58 (11.4%), Recovering 97 (19.1%), Recovered With Sequelae 13 (2.6%), and Unknown/missing 110 (21.7%).

The time to onset from the administration of vaccine to the onset of the CVST event was available in 371 (73%) case reports. The time to onset from the administration of vaccine to the CVST event onset was 0-7 days in 119 (32%), 8-14 days in 85 (23%), 15-21 days in 43 (11.6%), 22-28 days in 28 (7.9%), and greater than 28 days in 96 (25.9%) of cases. Time to onset was not reported in 137 (36.9%) cases. Time to onset ranged from 0 – 301 days with a median of 39 days.

There were 46 case reports in individuals who were reported to have received 2 doses of vaccine and the event occurred post 2nd dose. Most of the case reports 28 out of 46 (61%) occurred in vaccinees age group of 40 to 69 and 25 (54%) of the 46 cases were in female vaccinees. The time to onset was available in 41 case reports. The time to onset from the administration of vaccine to the event onset was 0-7 days in 8 (19.5%), 8-14 days in 5 (12.1%), 15-21 days in 4 (9.7%), 22-28 days in 3 (7.3%), and greater than 28 days in 21 (51.2%) of cases. Time to onset was not reported in 5 (12.1%) cases. There were 4 reported fatal cases out of 46 case reports in patient who had 2nd dose. Of the 4 deaths, 3 were vaccinees aged <40 years and in 1 report age was >60. Reported age in the four fatal cases was 28, 28, 38 and 63 years respectively. Reported causes of death in the 4 reports were: Cerebral venous sinus thrombosis (3) and Cavernous sinus thrombosis.

There were 2 case reports in individuals who were reported to have received a booster dose of vaccine and the event occurred post booster dose. The time to onset from the administration was 8 days in one case and the time to onset was not reported in the second booster case. Reported cause of death for the both booster dose cases was Cerebral venous thrombosis as described below:

- PPD : PPD year old PPD who was reported to have received COVID vaccine Dose 1 and Dose 2 (COVID-19 VACCINE PFIZER) and Dose 3b (COVID-19 VACCINE ASTRA ZENECA), all on the same date PPD) and patient experienced cerebral venous thrombosis (preferred term: Cerebral venous thrombosis) on PPD (Time to onset-18 days).
- PPD : PPD year old PPD who was reported to have received Dose 1 and Dose 2 (COVID-19 VACCINE ASTRA ZENECA) on the same date PPD and Dose 3b (COVID-19 VACCINE PFIZER) on PPD and on an unknown date, patient experienced cerebral venous thrombosis (preferred term: Cerebral venous thrombosis).

There were no case reports with positive rechallenge (after the first and second dose of the vaccine).

Radiological confirmation of CVST diagnosis was available in 189 (37.2%) of the 508 cases.

Cumulatively, 2 cases (PPD) were reported where patient experienced CVST after receiving the COVID-19 messenger RNA (mRNA) Vaccine Biontech (tozinameran) as dose 2, and where dose 1 was COVID-19 VACCINE ASTRAZENECA.

There was available information on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 126 (24%) of the 508 cases. A single case may have more than one risk/confounding factor. Details of the risk factors for the cases are provided in Table 117.

Table 117 Risk/confounding factors

Risk Factor	Case Count
Contraceptive use	41
Cancer	22
Past history of Obesity	12
Deep Vein Thrombosis	10
History of Thrombosis	10
COVID-19 illness prior to vaccine	5
Factor V Leiden mutation	5
Hypertension	4
Pulmonary Embolism	4
Fibromyalgia	3
Immunodeficiency	3
Overweight	3
Autoimmune thyroiditis	2
Body mass index increased	2
Past drug therapy included heparin	2
Rheumatic arthritis	2
Rheumatic disorder	2
Systemic lupus erythematous	2
Abortion spontaneous	2
Antiphospholipid syndrome	1
Autoimmune disorder	1
Factor II deficiency	1
Chronic kidney disease	1
Diabetes mellitus	1
Drug hypersensitivity	1
Inflammatory bowel disease	1
Methotrexate use	1
Monoclonal gammopathy	1
Multiple Sclerosis	1
Polymyalgia rheumatica	1
Sarcoidosis	1
Vasculitis	1

WHO-UMC criteria was used to perform causality assessment. Of the 508 cases reported there was 1 case report which met the causality term Conditional/Unclassified, 183 case reports which met the causality term Unassessable/Unclassifiable, 68 case reports which met the causality term Unlikely and 255 case reports which met the causality term Possible and 1 case report which met

the causality term Likely. None of the cases met WHO-UMC criteria for Certain. For 69 of the 255 cases with Possible causality, the assessment was based on a reasonable TTO, although the events could also be explained by the vaccinees' medical history and/or comorbidities; the remaining 186 cases were classified as possible due to temporal association, with limited or no information available on the vaccinees' medical history, comorbidities, concomitant medications, etc. The 1 case assessed as "Likely" related is discussed below.

PPD : (Dutta et al 2021) A case of a PPD-year-old adult PPD patient with no comorbidity and reportedly not on any medications, received the first-dose of COVISHIELD. PPD reportedly experienced headache with intermittent and spontaneous vomiting 6 days later. PPD had intermittent relief from PPD reportedly started complaining of double vision which appeared in horizontal gaze (double vision in right gaze was more than that of left gaze) 12 days from the onset of headache. PPD reportedly noticed loss of parallelism of PPD eyeballs in neutral position. PPD was hospitalized 12 days after the onset of headache. There was no reported history of convulsion, diminution of vision or focal weakness or past COVID-19 infection. There was no reported history of cranio-cervical trauma or infection in recent or remote past. Neurological examination was significant for presence of PPD . Other systemic and neurologic examinations were non-contributory Ophthalmoscopic examination revealed bilateral grade-2 papilledema. Magnetic resonance imaging (MRI) of brain with contrast revealed no intraparenchymal lesion. MR venography revealed thrombosis in superior sagittal sinus and transverse sinus with presence of extensive venous collaterals. Systemic risk factors for development of Continuously variable transmission (CVT) (ie,), myeloproliferative disorders, malignancies, neuroinflammatory pathologies (sarcoidosis, Behcet's disease, and systemic lupus erythematosus), antiphospholipid antibody syndrome, and thyroid disorders were excluded after relevant investigations. Complete hemogram, blood sugar, lipid profiles, liver and kidney function tests were normal. Tests for known genetic causes of thrombophilia had a negative result (protein C, protein S, anti-thrombin III, homocysteine levels were normal; factor V Leiden mutation was not detected). Serologies for Human immunodeficiency virus (HIV) (1, 2), hepatitis B and C were nonreactive. Electrocardiogram (EKG) and echocardiography were normal. Considering the temporal association and potential thrombotic potential of COVISHIELD vaccine, a probable diagnosis of vaccine induced CVT was made by the reporter. However, repeated tests for detection of thrombocytopenia and anti-PF4-antibodies were futile and thus a diagnosis of vaccine-induced thrombotic thrombocytopenia VITT could not be made. Other relevant investigations conclusively ruled out other systemic thromboses (ie, pulmonary thromboembolism, splanchnic/abdominal thromboses, and thromboses involving the limbs). Patient was immediately put on PPD for 14 days; considering normal platelet count and PPD) with strict monitoring of activated partial thromboplastin time, prothrombin time international normalized ratio and D dimer. It was followed by addition of PPD from day 9 of PPD without any new complications. Patient was followed up for 3 weeks in inpatient care with significant improvement in PPD clinical status. Headache and papilledema had subsided completely in 1 week and 2 weeks, respectively, following

anticoagulation therapy. Double vision and extraocular movements had improved remarkably after 3 weeks. Patient had been kept under close follow up.

AstraZeneca Comment: The case has a Time to onset (TTO) of 6 days, medical history, concomitant medications and investigations suggests that the event of CVST without thrombocytopenia is unlikely could not be attributed to any disease or other drugs.

Review of Cases: Clinical-trial data

There was 1 report of Cerebral venous/Cerebral venous sinus thrombosis identified in the AZD1222 group in AstraZeneca sponsored study D8110C00001.

No reports of Cerebral venous/Cerebral venous sinus thrombosis identified in the AZD1222 group in AstraZeneca sponsored studies D8111C00002 or University of Oxford sponsored studies COV001, COV002, COV003 and COV005.

A search of the AstraZeneca global safety database through 30 November 2021 was conducted using the Preferred Terms under the HLT: Cerebrovascular and venous thrombosis from clinical trials. One case report including one SAE was identified and is discussed below:

PPD **:** Report involving a PPD-year-old PPD patient from PPD. Current medical history included hypothyroidism and rhinitis. Concomitant medications included PPD The subject received study therapy AZD1222 (Dose 1) on PPD and Dose 2 on PPD. Following second AZD1222 vaccine, patient experienced progressive bifrontal headache, which was treated with analgesia and PPD. Symptoms progressed and PPD reported drowsiness and PPD. On PPD, nearly 9 months after last vaccination with COVID-19VACCINE ASTRAZENECA, the patient experienced grade three, serious CVST, which was confirmed via MRI. Treatment included thrombectomy, PPD (current anticoagulant). The subject recovered from the event after 1 week. The Investigator considered that there was a reasonable possibility of a causal relationship between AZD1222 and CVST. AstraZeneca does not consider a reasonable possibility of a causal relationship between AZD1222 and CVST as the event occurred 301 days (43 weeks) after first dose and 270 days after second dose of COVID-19 VACCINE ASTRAZENECA. Furthermore, the subject's use of PPD is a confounding factor in the development of CVST.

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of CVST without thrombocytopenia (including all cases with platelet count more than 150,000 per microliter and also unknown platelet count) is presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 118 and stratified by age for the EEA region in Table 119 and stratified by age and gender for UK region in Table 120. The incidence rates used were from SIDIAP PCHOSP (Willame et al 2021 [B]), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca.

Table 118 Observed vs expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rate) for global reports

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	0.72	291626957	246	120.73	2.04 (1.79 - 2.31)	Observed significantly > expected	285	172.46	1.65 (1.47 – 1.86)	Observed significantly > expected	327	241.45	1.35 (1.21 – 1.51)	Observed significantly > expected
Overall (Global) plus cases Unk TTO	0.72	291626957	383	120.73	3.17 (2.86 – 3.51)	Observed significantly > expected	422	172.46	2.45 (2.22 – 2.69)	Observed significantly > expected	464	241.45	1.92 (1.75 - 2.1)	Observed significantly > expected

[a] Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP.

CI Confidence Interval, CVST Cerebral venous sinus thrombosis, E Expected; IR Incidence Rate; O Observed; TTO Time To Onset; Unk Unknown

Table 119 Observed vs expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA Data														

Table 119 Observed vs expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49 Years EEA	0.27	11515409	75	1.79	41.9 (32.96 - 52.52)	Observed significantly > expected	82	2.55	32.16 (25.58 - 39.92)	Observed significantly > expected	92	3.58	25.7 (20.72 - 31.52)	Observed significantly > expected
50-59 Years EEA	1.57	6275981	33	5.67	5.82 (4.01 - 8.17)	Observed significantly > expected	39	8.09	4.82 (3.43 - 6.59)	Observed significantly > expected	41	11.33	3.62 (2.6 - 4.91)	Observed significantly > expected
60-69 Years EEA	0.68	18684704	37	7.31	5.06 (3.56 - 6.98)	Observed significantly > expected	41	10.44	3.93 (2.82 - 5.33)	Observed significantly > expected	47	14.61	3.22 (2.36 - 4.28)	Observed significantly > expected
70-79 Years EEA	0.67	8010180	19	3.09	6.15 (3.7 - 9.6)	Observed significantly > expected	23	4.41	5.22 (3.31 - 7.83)	Observed significantly > expected	23	6.17	3.73 (2.36 - 5.59)	Observed significantly > expected

Table 119 Observed vs expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 80 Years EEA	1.49	1094043	2	0.94	2.13 (0.26 - 7.69)	Observed > expected	3	1.34	2.24 (0.46 - 6.54)	Observed > expected	4	1.87	2.14 (0.58 - 5.48)	Observed > expected

[a] Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP.

CI Confidence Interval, CVST Cerebral venous sinus thrombosis, E Expected; EEA European Economic Area, IR Incidence Rate; O Observed; TTO Time To Onset.

Table 120 Observed versus expected analysis for Cerebrovascular and venous thrombosis without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender in the United Kingdom

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 40 to 49 UK	0.77	4974220	11	2.2	5 (2.5 - 8.95)	Observed significantly > expected	11	3.15	3.49 (1.74 - 6.25)	Observed significantly > expected	12	4.4	2.73 (1.41 - 4.76)	Observed significantly > expected

Table 120 Observed versus expected analysis for Cerebrovascular and venous thrombosis without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender in the United Kingdom

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female over 80 UK	1.67	1721795	1	1.65	0.61 (0.02 - 3.38)	Observed < expected	1	2.36	0.42 (0.01 - 2.36)	Observed < expected	3	3.31	0.91 (0.19 - 2.65)	Observed < expected
Male 18 to 29 UK	1.27	986375	2	0.72	2.78 (0.34 - 10.03)	Observed > expected	2	1.03	1.94 (0.24 - 7.01)	Observed > expected	4	1.44	2.78 (0.76 - 7.11)	Observed > expected
Male 40 to 49 UK	0.72	5220928	5	2.16	2.31 (0.75 - 5.4)	Observed > expected	6	3.09	1.94 (0.71 - 4.23)	Observed > expected	7	4.32	1.62 (0.65 - 3.34)	Observed > expected
Male 50 to 59 UK	0.9	6957211	6	3.6	1.67 (0.61 - 3.63)	Observed > expected	8	5.14	1.56 (0.67 - 3.07)	Observed > expected	12	7.2	1.67 (0.86 - 2.91)	Observed > expected
Male 60 to 69 UK	2.49	4966917	4	7.11	0.56 (0.15 - 1.44)	Observed < expected	4	10.16	0.39 (0.11 - 1.01)	Observed < expected	6	14.22	0.42 (0.15 - 0.92)	Observed significantly < expected

Table 120 Observed versus expected analysis for Cerebrovascular and venous thrombosis without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender in the United Kingdom

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 70 to 79 UK	1.68	3223317	3	3.11	0.96 (0.2 - 2.82)	Observed < expected	3	4.45	0.67 (0.14 - 1.97)	Observed < expected	3	6.23	0.48 (0.1 - 1.41)	Observed < expected
Male over 80 UK	2.81	1042292	1	1.68	0.6 (0.02 - 3.32)	Observed < expected	1	2.41	0.41 (0.01 - 2.31)	Observed < expected	1	3.37	0.3 (0.01 - 1.65)	Observed < expected

Exposure until 28 December 2021

[a] Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, E Expected, IR Incidence Rate; O Observed; UK United Kingdom.

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. That approach is aligned with incidence rates routinely used for TTS O/E monitoring. In particular, the time window for exclusion of patients with TCP (-1/+14) was consistent with the one used for TTS. In this analysis a conservative approach in terms of ICD10 codes for CVST (I63.6 and I67.6) was used. Also the analysis included only incident (no CVST claims within 12 months prior to index) inpatient claims. Those analyses for CVST are presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 121 and stratified by age in the EEA in Table 122 and by age and gender in the UK in Table 123.

Table 121 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for global reports

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days					Risk Window 42 Days		
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	1.5	291626957	246	251.51	0.98 (0.86 - 1.11)	Observed < expected	285	359.3	0.79 (0.7 - 0.89)	Observed significantly < expected	327	503.02	0.65 (0.58 - 0.72)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	1.5	291626957	383	251.51	1.52 (1.37 - 1.68)	Observed significantly > expected	422	359.3	1.17 (1.07 - 1.29)	Observed significantly > expected	464	503.02	0.92 (0.84 - 1.01)	Observed < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019).

CI Confidence Interval, CVST Cerebral Venous Sinus Thrombosis; E Expected, IR Incidence Rate; O Observed; TTO Time to onset; Unk Unknown

Table 122 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18 to 49 EEA	1.55	11515409	75	10.26	7.31 (5.75 - 9.16)	Observed significantly > expected	82	14.66	5.59 (4.45 - 6.94)	Observed significantly > expected	92	20.52	4.48 (3.61 - 5.5)	Observed significantly > expected
50 to 59 EEA	0.86	6275981	33	3.1	10.65 (7.33 - 14.95)	Observed significantly > expected	39	4.43	8.8 (6.26 - 12.03)	Observed significantly > expected	41	6.21	6.6 (4.74 - 8.96)	Observed significantly > expected
60 to 69 EEA	1.65	18684704	37	17.73	2.09 (1.47 - 2.88)	Observed significantly > expected	41	25.32	1.62 (1.16 - 2.2)	Observed significantly > expected	47	35.45	1.33 (0.97 - 1.76)	Observed > expected
70 to 79 EEA	1.53	8010180	19	7.05	2.7 (1.62 - 4.21)	Observed significantly > expected	23	10.07	2.28 (1.45 - 3.43)	Observed significantly > expected	23	14.09	1.63 (1.03 - 2.45)	Observed significantly > expected
Over 80 EEA	8.21	1094043	2	5.16	0.39 (0.05 - 1.4)	Observed <	3	7.38	0.41 (0.08 - 1.19)	Observed <	4	10.33	0.39 (0.11 - 0.99)	Observed significa

Table 122 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
						expected				expected				ntly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, CVST Cerebral Venous Sinus Thrombosis; E Expected, EEA European Economic Area, IR Incidence Rate, O Observed

Table 123 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 18 to 29 UK	2.46	1339334	3	1.89	1.59 (0.33 - 4.64)	Observed > expected	4	2.71	1.48 (0.4 - 3.78)	Observed > expected	4	3.79	1.06 (0.29 - 2.7)	Observed > expected
Female 30 to 39 UK	2.23	2096348	3	2.69	1.12 (0.23 - 3.26)	Observed > expected	3	3.84	0.78 (0.16 - 2.28)	Observed < expected	5	5.38	0.93 (0.3 - 2.17)	Observed < expected

Table 123 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 40 to 49 UK	1.84	4974220	11	5.26	2.09 (1.04 - 3.74)	Observed significantly > expected	11	7.52	1.46 (0.73 - 2.62)	Observed > expected	12	10.52	1.14 (0.59 - 1.99)	Observed > expected
Female 50 to 59 UK	0.82	6319086	6	2.98	2.01 (0.74 - 4.38)	Observed > expected	8	4.26	1.88 (0.81 - 3.7)	Observed > expected	9	5.96	1.51 (0.69 - 2.87)	Observed > expected
Female 60 to 69 UK	1.41	4859019	2	3.94	0.51 (0.06 - 1.83)	Observed < expected	4	5.63	0.71 (0.19 - 1.82)	Observed < expected	5	7.88	0.63 (0.21 - 1.48)	Observed < expected
Female 70 to 79 UK	0.71	3562147	3	1.45	2.07 (0.43 - 6.05)	Observed > expected	4	2.08	1.92 (0.52 - 4.92)	Observed > expected	4	2.91	1.37 (0.37 - 3.52)	Observed > expected
Female over 80 UK	9.32	1721795	1	9.23	0.11 (0 - 0.6)	Observed significantly <	1	13.18	0.08 (0 - 0.42)	Observed significantly <	3	18.45	0.16 (0.03 - 0.48)	Observed significantly < expected

Table 123 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
						expected				expected				
Male 18 to 29 UK	1.1	986375	2	0.62	3.23 (0.39 - 11.65)	Observed > expected	2	0.89	2.25 (0.27 - 8.12)	Observed > expected	4	1.25	3.2 (0.87 - 8.19)	Observed > expected
Male 30 to 39 UK	0.69	1582807	2	0.63	3.17 (0.38 - 11.47)	Observed > expected	2	0.9	2.22 (0.27 - 8.03)	Observed > expected	2	1.26	1.59 (0.19 - 5.73)	Observed > expected
Male 40 to 49 UK	0.86	5220928	5	2.58	1.94 (0.63 - 4.52)	Observed > expected	6	3.69	1.63 (0.6 - 3.54)	Observed > expected	7	5.16	1.36 (0.55 - 2.8)	Observed > expected
Male 50 to 59 UK	0.91	6957211	6	3.64	1.65 (0.6 - 3.59)	Observed > expected	8	5.2	1.54 (0.66 - 3.03)	Observed > expected	12	7.28	1.65 (0.85 - 2.88)	Observed > expected
Male 60 to 69 UK	1.92	4966917	4	5.48	0.73 (0.2 - 1.87)	Observed < expected	4	7.83	0.51 (0.14 - 1.31)	Observed < expected	6	10.97	0.55 (0.2 - 1.19)	Observed < expected

Table 123 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 70 to 79 UK	2.49	3223317	3	4.61	0.65 (0.13 - 1.9)	Observed < expected	3	6.59	0.46 (0.09 - 1.33)	Observed < expected	3	9.23	0.33 (0.07 - 0.95)	Observed significantly < expected
Male over 80 UK	6.64	1042292	1	3.98	0.25 (0.01 - 1.4)	Observed < expected	1	5.68	0.18 (0 - 0.98)	Observed significantly < expected	1	7.96	0.13 (0 - 0.7)	Observed significantly < expected

Exposure until 28 December 2021

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, E Expected, IR Incidence Rate, O Observed, UK United Kingdom.

When an overall rate of 0.72/100,000 person years from SIDIAP_HOSP is used, observed cases of CVST without thrombocytopenia are significantly more than expected for all risk windows. This is regardless of whether cases with an unknown time to onset are included or excluded. In comparison, when Truven 14 IR are used, observed cases are less than expected for all the risk windows, when cases with unknown TTO are excluded. When cases with an unknown TTO are included to all risk windows as a conservative approach, observed cases are significantly more than expected for 21 and 30 day risk windows but observed cases were less than expected for 42 day risk window Table 121.

When the observed versus expected analysis was stratified by age in the EEA region using SIDIAP_HOSP rates, observed cases were either more or significantly more than expected for age stratifications and all risk windows (21, 30 and 42 days) Table 119. When Truven 14 IRs was were used, observed cases are significantly more than expected in all age groups from 18-79 years for risk windows 21 and 30 days and for age groups 18-59 and 70-79 years for risk window 42 days. For the age group 60-69 years and risk window 42, observed cases were more than expected, however the result was not significant. Observed cases were less than expected for age 80 years and older for all risk windows, the result was significantly less than expected for risk window 42 days Table 122.

When stratified by age and gender in the UK, using SIDIAP_HOSP and Truven 14 IRs, the observed cases divide between males and females as follows.

For females the results with SIDIAP_HOSP Table 120 were provided only for 40-49 and over 80 years age groups (background rates are not available for other age groups), for 40-49 years age group observed cases were significantly more than expected for all risk windows (21, 30 and 42 days), and for over 80 years age group, observed cases were less than expected for all risk windows (21, 30 and 42 days). In comparison, when Truven 14 IR Table 123 are used results for all the age groups were available. Observed cases are only significantly more than expected for the age group 40-49 years and 21 days risk window. Observed cases were significantly less than expected in age group 80 years and over for all risk windows. For all other age stratifications observed cases were either more or less than expected, with a tendency to have a higher O/E ratio in the lower age ranges and shorter risk windows than in the higher age ranges.

For males, the results were similar with both SIDIAP_HOSP Table 120 and Truven 14 IRs Table 123. For the younger age groups 18-59 and all three risk windows (21, 30 and 42 days), observed cases were more than expected for both IRs, however the results were not significant. Observed cases were less than expected for all age groups 60 years and older for all risk windows (21, 30 and 42 days). For Truven 14 IR observed cases were significantly less than expected for over 80 years age group for all risk windows (21, 30 and 42 days). For all other age stratifications observed cases were either more or less than expected, with a tendency to have a higher O/E ratio in the lower age ranges and shorter risk windows than in the higher age ranges.

Observed versus expected analyses for CVST without thrombocytopenia (with known normal platelet count)

Information on normal platelets was available in 117 of the 508 cases. In the remaining 391 of the 508 cases the post-vaccination platelet count was unknown, however no thrombocytopenia-related PTs were reported. The 117 cases were used for observed versus expected analysis in order to represent the dataset with known normal thrombocytes.

The observed versus expected analysis for all 117 cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for global reports in Table 124 and stratified by age in the EEA/UK region in Table 125. The incidence rates used were from SIDIAP PCHOSP (Willame et al 2021 [B]), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca. All stratifications are provided with and without cases that have an unknown time to onset.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases was lower than expected when all cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 124 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate) for global reports

Age group/ Gender	IR[a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	0.72	291626957	46	120.73	0.38 (0.28 - 0.51)	Observed significantly < expected	60	172.46	0.35 (0.27 - 0.45)	Observed significantly < expected	72	241.45	0.3 (0.23 - 0.38)	Observed significantly < expected
Overall (Global) including cases with an unknown time to onset	0.72	291626957	72	120.73	0.6 (0.47 - 0.75)	Observed significantly < expected	86	172.46	0.5 (0.4 - 0.62)	Observed significantly < expected	98	241.45	0.41 (0.33 - 0.49)	Observed significantly < expected

[a] Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed

Table 125 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA Data														
18-49 Years EEA	0.34	11515409	5	2.25	2.22 (0.72 - 5.19)	Observed > expected	6	3.22	1.86 (0.68 - 4.06)	Observed > expected	6	4.5	1.33 (0.49 - 2.9)	Observed > expected
50-59 Years EEA	1.57	6275981	3	5.67	0.53 (0.11 - 1.55)	Observed < expected	5	8.09	0.62 (0.2 - 1.44)	Observed < expected	5	11.33	0.44 (0.14 - 1.03)	Observed < expected
60-69 Years EEA	0.68	18684704	3	7.31	0.41 (0.08 - 1.2)	Observed < expected	3	10.44	0.29 (0.06 - 0.84)	Observed significantly < expected	4	14.61	0.27 (0.07 - 0.7)	Observed significantly < expected
70-79 Years EEA	0.67	8010180	1	3.09	0.32 (0.01 - 1.8)	Observed < expected	3	4.41	0.68 (0.14 - 1.99)	Observed < expected	3	6.17	0.49 (0.1 - 1.42)	Observed < expected
Over 80 Years EEA	1.49	1094043	0	0.94	0 (0 - 3.92)	Observed < expected	0	1.34	0 (0 - 2.75)	Observed < expected	1	1.87	0.53 (0.01 - 2.98)	Observed < expected

Table 125 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49 Years EEA plus unknown TTO	0.34	11515409	7	2.25	3.11 (1.25 - 6.41)	Observed significantly > expected	8	3.22	2.48 (1.07 - 4.9)	Observed significantly > expected	8	4.5	1.78 (0.77 - 3.5)	Observed > expected
50-59 Years EEA plus unknown TTO	1.57	6275981	3	5.67	0.53 (0.11 - 1.55)	Observed < expected	5	8.09	0.62 (0.2 - 1.44)	Observed < expected	5	11.33	0.44 (0.14 - 1.03)	Observed < expected
60-69 Years EEA plus unknown TTO	0.68	18684704	3	7.31	0.41 (0.08 - 1.2)	Observed < expected	3	10.44	0.29 (0.06 - 0.84)	Observed significantly < expected	4	14.61	0.27 (0.07 - 0.7)	Observed significantly < expected
70-79 Years EEA plus unkno	0.67	8010180	2	3.09	0.65 (0.08 - 2.34)	Observed < expected	4	4.41	0.91 (0.25 - 2.32)	Observed < expected	4	6.17	0.65 (0.18 - 1.66)	Observed < expected

Table 125 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
wn TTO														
Over 80 Years EEA plus unknown TTO	1.49	1094043	0	0.94	0 (0 - 3.92)	Observed < expected	0	1.34	0 (0 - 2.75)	Observed < expected	1	1.87	0.53 (0.01 - 2.98)	Observed < expected
UK Data														
18 to 49 UK	0.34	27716022	12	5.42	2.21 (1.14 - 3.87)	Observed significantly > expected	13	7.74	1.68 (0.89 - 2.87)	Observed > expected	15	10.84	1.38 (0.77 - 2.28)	Observed > expected
50 to 59 UK	1.57	19552392	9	17.65	0.51 (0.23 - 0.97)	Observed significantly < expected	12	25.21	0.48 (0.25 - 0.83)	Observed significantly < expected	14	35.3	0.4 (0.22 - 0.67)	Observed significantly < expected

Table 125 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
60 to 69 UK	0.68	28510714	3	11.15	0.27 (0.06 - 0.79)	Observed significantly < expected	5	15.92	0.31 (0.1 - 0.73)	Observed significantly < expected	7	22.29	0.31 (0.13 - 0.65)	Observed significantly < expected
70 to 79 UK	0.67	14795684	4	5.7	0.7 (0.19 - 1.8)	Observed < expected	5	8.14	0.61 (0.2 - 1.43)	Observed < expected	5	11.4	0.44 (0.14 - 1.02)	Observed < expected
Over 80 UK	1.49	3858135	1	3.31	0.3 (0.01 - 1.68)	Observed < expected	1	4.72	0.21 (0.01 - 1.18)	Observed < expected	3	6.61	0.45 (0.09 - 1.33)	Observed < expected
18 to 49 UK plus unknown TTO	0.34	27716022	16	5.42	2.95 (1.69 - 4.79)	Observed significantly > expected	17	7.74	2.2 (1.28 - 3.52)	Observed significantly > expected	19	10.84	1.75 (1.06 - 2.74)	Observed significantly > expected
50 to 59 UK plus unkno	1.57	19552392	13	17.65	0.74 (0.39 - 1.26)	Observed < expected	16	25.21	0.63 (0.36 - 1.03)	Observed < expected	18	35.3	0.51 (0.3 - 0.81)	Observed significantly < expected

Table 125 Observed Vs expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
wn TTO														
60 to 69 UK plus unknown TTO	0.68	28510714	5	11.15	0.45 (0.15 - 1.05)	Observed < expected	7	15.92	0.44 (0.18 - 0.91)	Observed significantly < expected	9	22.29	0.4 (0.18 - 0.77)	Observed significantly < expected
70 to 79 UK plus unknown TTO	0.67	14795684	5	5.7	0.88 (0.28 - 2.05)	Observed < expected	6	8.14	0.74 (0.27 - 1.6)	Observed < expected	6	11.4	0.53 (0.19 - 1.15)	Observed < expected
Over 80 UK plus unknown TTO	1.49	3858135	2	3.31	0.6 (0.07 - 2.18)	Observed < expected	2	4.72	0.42 (0.05 - 1.53)	Observed < expected	4	6.61	0.61 (0.16 - 1.55)	Observed < expected

Exposure until 28 December 2021

[a] Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected, EEA European Economic Area, IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom;.

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. That approach is aligned with incidence rates routinely used for TTS O/E monitoring. In particular, the time window for exclusion of patients with TCP (either -7/+7 or-1/+14) was consistent with the one used for TTS. In this analysis, a conservative approach in terms of ICD10 codes for CVST (I63.6 and I67.6) was used. Also, the analysis included only incident (no CVST claims within 12 months prior to index) inpatient claims. Those analyses for CVST are presented with different risk windows (21 days, 30 days, and 42 days) for all global reports in Table 126, stratified by age in the EEA/UK in Table 127 and stratified by age and gender in the UK Table 128. All stratifications also included cases with an unknown TTO, as a conservative approach.

Table 126 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for global reports

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	1.5	291626957	46	251.51	0.18 (0.13 - 0.24)	Observed significantly < expected	60	359.3	0.17 (0.13 - 0.21)	Observed significantly < expected	72	503.02	0.14 (0.11 - 0.18)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	1.5	291626957	72	251.51	0.29 (0.22 - 0.36)	Observed significantly < expected	86	359.3	0.24 (0.19 - 0.3)	Observed significantly < expected	98	503.02	0.19 (0.16 - 0.24)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within *--1/+14* days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; Unk Unknown

Table 127 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for EEA and UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA data														
18 to 49 EEA	1.55	11515409	5	10.26	0.49 (0.16 - 1.14)	Observed < expected	6	14.66	0.41 (0.15 - 0.89)	Observed significantly < expected	6	20.52	0.29 (0.11 - 0.64)	Observed significantly < expected
50 to 59 EEA	0.86	6275981	3	3.1	0.97 (0.2 - 2.83)	Observed < expected	5	4.43	1.13 (0.37 - 2.63)	Observed > expected	5	6.21	0.81 (0.26 - 1.88)	Observed < expected
60 to 69 EEA	1.65	18684704	3	17.73	0.17 (0.03 - 0.49)	Observed significantly < expected	3	25.32	0.12 (0.02 - 0.35)	Observed significantly < expected	4	35.45	0.11 (0.03 - 0.29)	Observed significantly < expected
70 to 79 EEA	1.53	8010180	1	7.05	0.14 (0 - 0.79)	Observed significantly < expected	3	10.07	0.3 (0.06 - 0.87)	Observed significantly < expected	3	14.09	0.21 (0.04 - 0.62)	Observed significantly < expected

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 80 EEA	8.21	1094043	0	5.16	0 (0 - 0.71)	Observed significantly < expected	0	7.38	0 (0 - 0.5)	Observed significantly < expected	1	10.33	0.1 (0 - 0.54)	Observed significantly < expected
18 to 49 EEA plus unknown TTO	1.55	11515409	7	10.26	0.68 (0.27 - 1.41)	Observed < expected	8	14.66	0.55 (0.24 - 1.08)	Observed < expected	8	20.52	0.39 (0.17 - 0.77)	Observed significantly < expected
50 to 59 EEA plus unknown TTO	0.86	6275981	3	3.1	0.97 (0.2 - 2.83)	Observed < expected	5	4.43	1.13 (0.37 - 2.63)	Observed > expected	5	6.21	0.81 (0.26 - 1.88)	Observed < expected
60 to 69 EEA plus unknown TTO	1.65	18684704	3	17.73	0.17 (0.03 - 0.49)	Observed significantly < expected	3	25.32	0.12 (0.02 - 0.35)	Observed significantly < expected	4	35.45	0.11 (0.03 - 0.29)	Observed significantly < expected

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
70 to 79 EEA plus unknown TTO	1.53	8010180	2	7.05	0.28 (0.03 - 1.02)	Observed < expected	4	10.07	0.4 (0.11 - 1.02)	Observed < expected	4	14.09	0.28 (0.08 - 0.73)	Observed significantly < expected
Over 80 EEA plus unknown TTO	8.21	1094043	0	5.16	0 (0 - 0.71)	Observed significantly < expected	0	7.38	0 (0 - 0.5)	Observed significantly < expected	1	10.33	0.1 (0 - 0.54)	Observed significantly < expected
UK data														
18 to 49 UK	1.55	16200613	12	14.44	0.83 (0.43 - 1.45)	Observed < expected	13	20.63	0.63 (0.34 - 1.08)	Observed < expected	15	28.88	0.52 (0.29 - 0.86)	Observed significantly < expected
50 to 59 UK	0.86	13276411	9	6.56	1.37 (0.63 - 2.6)	Observed > expected	12	9.38	1.28 (0.66 - 2.23)	Observed > expected	14	13.13	1.07 (0.58 - 1.79)	Observed > expected
60 to 69 UK	1.65	9826010	3	9.32	0.32 (0.07 - 0.94)	Observed signific	5	13.32	0.38 (0.12 - 0.88)	Observed signific	7	18.64	0.38 (0.15 - 0.77)	Observed significa

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
						antly < expected				antly < expected				ntly < expected
70 79 UK	1.53	6785504	4	5.97	0.67 (0.18 - 1.72)	Observed < expected	5	8.53	0.59 (0.19 - 1.37)	Observed < expected	5	11.94	0.42 (0.14 - 0.98)	Observed significantly < expected
Over 80 UK	8.21	2764092	1	13.05	0.08 (0 - 0.43)	Observed significantly < expected	1	18.64	0.05 (0 - 0.3)	Observed significantly < expected	3	26.1	0.11 (0.02 - 0.34)	Observed significantly < expected
18 to 49 UK plus unknown TTO	1.55	16200613	16	14.44	1.11 (0.63 - 1.8)	Observed > expected	17	20.63	0.82 (0.48 - 1.32)	Observed < expected	19	28.88	0.66 (0.4 - 1.03)	Observed < expected
50 to 59 UK plus unknown TTO	0.86	13276411	13	6.56	1.98 (1.06 - 3.39)	Observed significantly > expected	16	9.38	1.71 (0.97 - 2.77)	Observed > expected	18	13.13	1.37 (0.81 - 2.17)	Observed > expected

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
60 to 69 UK plus unknown TTO	1.65	9826010	5	9.32	0.54 (0.17 - 1.25)	Observed < expected	7	13.32	0.53 (0.21 - 1.08)	Observed < expected	9	18.64	0.48 (0.22 - 0.92)	Observed significantly < expected
70 79 UK plus unknown TTO	1.53	6785504	5	5.97	0.84 (0.27 - 1.95)	Observed < expected	6	8.53	0.7 (0.26 - 1.53)	Observed < expected	6	11.94	0.5 (0.18 - 1.09)	Observed < expected
Over 80 UK plus unknown TTO	8.21	2764092	2	13.05	0.15 (0.02 - 0.55)	Observed significantly < expected	2	18.64	0.11 (0.01 - 0.39)	Observed significantly < expected	4	26.1	0.15 (0.04 - 0.39)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

Truven 7: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 18 to 29 UK	2.46	1339334	1	1.89	0.53 (0.01 - 2.95)	Observed < expected	1	2.71	0.37 (0.01 - 2.06)	Observed < expected	1	3.79	0.26 (0.01 - 1.47)	Observed < expected
Female 30 to 39 UK	2.23	2096348	2	2.69	0.74 (0.09 - 2.69)	Observed < expected	2	3.84	0.52 (0.06 - 1.88)	Observed < expected	2	5.38	0.37 (0.05 - 1.34)	Observed < expected
Female 40 to 49 UK	1.84	4974220	4	5.26	0.76 (0.21 - 1.95)	Observed < expected	4	7.52	0.53 (0.14 - 1.36)	Observed < expected	5	10.52	0.48 (0.15 - 1.11)	Observed < expected
Female 50 to 59 UK	0.82	6319086	4	2.98	1.34 (0.37 - 3.44)	Observed > expected	5	4.26	1.17 (0.38 - 2.74)	Observed > expected	6	5.96	1.01 (0.37 - 2.19)	Observed > expected
Female 60 to 69 UK	1.41	4859019	1	3.94	0.25 (0.01 - 1.41)	Observed < expected	3	5.63	0.53 (0.11 - 1.56)	Observed < expected	4	7.88	0.51 (0.14 - 1.3)	Observed < expected

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 70 to 79 UK	0.71	3562147	2	1.45	1.38 (0.17 - 4.98)	Observed > expected	3	2.08	1.44 (0.3 - 4.22)	Observed > expected	3	2.91	1.03 (0.21 - 3.01)	Observed > expected
Female over 80 UK	9.32	1721795	0	9.23	0 (0 - 0.4)	Observed significantly < expected	0	13.18	0 (0 - 0.28)	Observed significantly < expected	2	18.45	0.11 (0.01 - 0.39)	Observed significantly < expected
Male 18 to 29 UK	1.1	986375	1	0.62	1.61 (0.04 - 8.99)	Observed > expected	1	0.89	1.12 (0.03 - 6.26)	Observed > expected	2	1.25	1.6 (0.19 - 5.78)	Observed > expected
Male 30 to 39 UK	0.69	1582807	1	0.63	1.59 (0.04 - 8.84)	Observed > expected	1	0.9	1.11 (0.03 - 6.19)	Observed > expected	1	1.26	0.79 (0.02 - 4.42)	Observed < expected

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 40 to 49 UK	0.86	5220928	3	2.58	1.16 (0.24 - 3.4)	Observed > expected	4	3.69	1.08 (0.3 - 2.78)	Observed > expected	4	5.16	0.78 (0.21 - 1.98)	Observed < expected
Male 50 to 59 UK	0.91	6957211	5	3.64	1.37 (0.45 - 3.21)	Observed > expected	7	5.2	1.35 (0.54 - 2.77)	Observed > expected	8	7.28	1.1 (0.47 - 2.17)	Observed > expected
Male 60 to 69 UK	1.92	4966917	2	5.48	0.36 (0.04 - 1.32)	Observed < expected	2	7.83	0.26 (0.03 - 0.92)	Observed significantly < expected	3	10.97	0.27 (0.06 - 0.8)	Observed significantly < expected
Male 70 to 79 UK	2.49	3223317	2	4.61	0.43 (0.05 - 1.57)	Observed < expected	2	6.59	0.3 (0.04 - 1.1)	Observed < expected	2	9.23	0.22 (0.03 - 0.78)	Observed significantly < expected

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male over 80 UK	6.64	1042292	1	3.98	0.25 (0.01 - 1.4)	Observed < expected	1	5.68	0.18 (0 - 0.98)	Observed significantly < expected	1	7.96	0.13 (0 - 0.7)	Observed significantly < expected
Female 18 to 29 UK plus unknown TTO	2.46	1339334	1	1.89	0.53 (0.01 - 2.95)	Observed < expected	1	2.71	0.37 (0.01 - 2.06)	Observed < expected	1	3.79	0.26 (0.01 - 1.47)	Observed < expected
Female 30 to 39 UK plus unknown TTO	2.23	2096348	2	2.69	0.74 (0.09 - 2.69)	Observed < expected	2	3.84	0.52 (0.06 - 1.88)	Observed < expected	2	5.38	0.37 (0.05 - 1.34)	Observed < expected
Female 40 to 49 UK plus unknown TTO	1.84	4974220	7	5.26	1.33 (0.54 - 2.74)	Observed > expected	7	7.52	0.93 (0.37 - 1.92)	Observed < expected	8	10.52	0.76 (0.33 - 1.5)	Observed < expected

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 50 to 59 UK plus unknown TTO	0.82	6319086	5	2.98	1.68 (0.54 - 3.92)	Observed > expected	6	4.26	1.41 (0.52 - 3.07)	Observed > expected	7	5.96	1.17 (0.47 - 2.42)	Observed > expected
Female 60 to 69 UK plus unknown TTO	1.41	4859019	3	3.94	0.76 (0.16 - 2.23)	Observed < expected	5	5.63	0.89 (0.29 - 2.07)	Observed < expected	6	7.88	0.76 (0.28 - 1.66)	Observed < expected
Female 70 to 79 UK plus unknown TTO	0.71	3562147	2	1.45	1.38 (0.17 - 4.98)	Observed > expected	3	2.08	1.44 (0.3 - 4.22)	Observed > expected	3	2.91	1.03 (0.21 - 3.01)	Observed > expected
Female over 80 UK plus unknown TTO	9.32	1721795	1	9.23	0.11 (0 - 0.6)	Observed significantly <	1	13.18	0.08 (0 - 0.42)	Observed significantly < expected	3	18.45	0.16 (0.03 - 0.48)	Observed significantly < expected

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
						expected								
Male 18 to 29 UK plus unknown TTO	1.1	986375	1	0.62	1.61 (0.04 - 8.99)	Observed > expected	1	0.89	1.12 (0.03 - 6.26)	Observed > expected	2	1.25	1.6 (0.19 - 5.78)	Observed > expected
Male 30 to 39 UK plus unknown TTO	0.69	1582807	1	0.63	1.59 (0.04 - 8.84)	Observed > expected	1	0.9	1.11 (0.03 - 6.19)	Observed > expected	1	1.26	0.79 (0.02 - 4.42)	Observed < expected
Male 40 to 49 UK plus unknown TTO	0.86	5220928	4	2.58	1.55 (0.42 - 3.97)	Observed > expected	5	3.69	1.36 (0.44 - 3.16)	Observed > expected	5	5.16	0.97 (0.31 - 2.26)	Observed < expected
Male 50 to 59 UK plus	0.91	6957211	8	3.64	2.2 (0.95 - 4.33)	Observed >	10	5.2	1.92 (0.92 - 3.54)	Observed >	11	7.28	1.51 (0.75 - 2.7)	Observed >

Table 128 Observed versus expected analysis for CVST (Cerebrovascular and venous thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age and gender in the UK

Age group/ Gender	IR [a]	Exposure	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
unknown TTO						expected				expected				expected
Male 60 to 69 UK plus unknown TTO	1.92	4966917	2	5.48	0.36 (0.04 - 1.32)	Observed < expected	2	7.83	0.26 (0.03 - 0.92)	Observed significantly < expected	3	10.97	0.27 (0.06 - 0.8)	Observed significantly < expected
Male 70 to 79 UK plus unknown TTO	2.49	3223317	3	4.61	0.65 (0.13 - 1.9)	Observed < expected	3	6.59	0.46 (0.09 - 1.33)	Observed < expected	3	9.23	0.33 (0.07 - 0.95)	Observed significantly < expected
Male over 80 UK plus unknown TTO	6.64	1042292	1	3.98	0.25 (0.01 - 1.4)	Observed < expected	1	5.68	0.18 (0 - 0.98)	Observed significantly < expected	1	7.96	0.13 (0 - 0.7)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

Truven 7: CVST (I63.6 or I67.6) inpatient without TCP within -7/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European Economic Area

Literature

A cumulative search of the Embase and InsightMeme.com databases through 28 December 2021 was undertaken using to identify literature of CVST with COVID-19 vaccines, including COVID-19 VACCINE ASTRAZENECA.

A total of 118 (109 from Embase and 9 from InsightMeme) search results were obtained. Of these, none identified any new safety information or discussions of mechanism of action relevant to the review of this topic.

Summary

Five hundred and eight cases with CVST without thrombocytopenia were received from vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 508 case reports, 1 case was from the clinical trial, 21 literature cases, 3 cases from non-interventional/post-marketing and 483 cases are from spontaneous sources.

In 18-49 age group, 78 % of cases reportedly occurred in females. Twenty-one fatal cases (57%) out of all 37 fatal cases (in all age groups) occurred in 18-49 age group. There were 11 (52%) fatal reports in females and 10 (48%) fatal reports in males in 18-49 age group. The time to onset from the administration of vaccine to the onset of CVST was within 28 days in 54% of case reports. Underlying cause/confounding factors were noted in 126 (24%) of cases. Contraceptive use was the most common confounding factor (41 cases out of 126 cases). There was one case report where the onset of PT occurred after the administration of booster (third) dose. The booster vaccine was mRNA (Pfizer-BioNTech) vaccine.

Although there are reports in the literature and AstraZeneca Safety database describing CVST without thrombocytopenia, there are still gaps in information regarding key factors to allow a better understanding of the reports (eg, missing platelet counts, PF-4 antibody titres, TTO, background thrombosis risks).

Out of total 508 cases reported, the WHO-UMC causality was assessed as follows. 255 (50.1%) case reports were assessed as Possible and in 186 (73%) of the 255 cases the assessment was based solely on the reasonable TTO parameter and no information was available on assessments of other etiologies, or the vaccinees' medical history, comorbidities, concomitant medications, etc. The remaining 69 (27%) cases this assessment was based on a reasonable TTO although the event could also be explained by the vaccinees' diseases; The 0.1% case reports were assessed as Likely and another 0.1% case reports were assessed as Conditional/Unclassified, 36.3% of case reports were assessed as Unassessable/Unclassifiable and 13.4% case reports were assessed as Unlikely. None of the cases met WHO-UMC criteria for Certain.

The potential mechanism for TTS (including CVST with thrombocytopenia) is discussed in Section 16.3.2.1. There are several well-established risk factors for CVST, that include pregnancy and the peri-partum period, hormonal therapy (including oral contraceptives), obesity, inflammation, inherited and acquired thrombophilia, nephrotic syndrome, hematologic disorders, malignancies, regional infections, procedures in the area, dehydration and sickle cell disease. COVID-19 infection can cause CVST as well. These risk factors are applicable for CVST with or without thrombocytopenia.

The results of the O/E analyses with all CVST without thrombocytopenia (with known normal and unknown platelet counts) suggest that observed cases are more than would be expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is suggestively higher in females than in males. However, the O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases was lower than expected when all cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, the amount of missing information prohibited a meaningful medical assessment of these cases.

The presence of CVST without thrombocytopenia may represent a different pathology from CVST with thrombocytopenia. While mechanisms are being explored AstraZeneca will continue to monitor these cases closely.

Conclusion

Based on the currently available data, AstraZeneca considers that there is currently insufficient evidence of a causal relationship between COVID-19 VACCINE ASTRAZENECA and CVST without thrombocytopenia.

Due to potential differences in treatment choices and management of CVST without thrombocytopenia (eg, use of heparin or warfarin), there is a need to differentiate this condition from CVST in combination with thrombocytopenia. Therefore, COVID-19 VACCINE ASTRAZENECA CDS, section 4.4 Warnings and Precautions was updated on 02 November 2021 (see Section 5.2). In addition, CVST without thrombocytopenia was added as an Important potential risk in the COVID-19 RMP during the review period (See Section 16.2.2).

CVST without thrombocytopenia will continue to be kept under close surveillance by AstraZeneca.

More detailed information regarding this important potential risk is provided in Section 16.4.2

16.3.2 New information on important identified risks

All Important identified risks included in Section 16.1 and included in Table 129 below are kept under close surveillance by AstraZeneca.

Table 129 Important identified risks presented in Core RMP (Version 3.0; dated 28 April 2021)

Section/Topic	Core RMP
Important identified risk	Thrombosis in combination with thrombocytopenia

RMP Risk Management Plan.

16.3.2.1 Thrombosis in combination with thrombocytopenia / Thrombosis with thrombocytopenia syndrome

Review of Cases

A cumulative search of the AstraZeneca safety database was undertaken for AE reports under the HLT: Thrombocytopenia and SMQ: Hematopoietic Thrombocytopenia Narrow co-reported with events identified from the SMQ: Embolic and thrombotic events with COVID-19 VACCINE ASTRAZENECA. This search criteria was also applied to retrieve case reports of Thrombosis with thrombocytopenia syndrome (TTS) following both first and second dose of COVID-19 VACCINE ASTRAZENECA. Also, cases with a reported PT of Thrombosis with Thrombocytopenia Syndrome (TTS) or Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) or Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) were included, as there is now corresponding PTs in MedDRA version 24.1. Also, cases of CVST from Section 16.3.1.3 with platelet count less than 150 x10^9/ L were included. This covered the period up to 28 December 2021.

The search resulted in a total of 2060 individual closed cases (cumulative up to 28 December 2021), and one case was considered as potential duplicate on further review. The below analysis was focused on 2059 unique reports. Of the 2059 cases, 2051 were serious and 8 were non serious, 1444 case reports were medically confirmed and 615 were consumer reports and 1617 case reports were from regulatory, 272 from spontaneous and 170 from literature sources. There were 211 cases reported with thrombosis in combination with thrombocytopenia after confirmed Dose 2. There were 27 cases where the Embolic and thrombotic event was not reported.

During the reporting interval (29 June 2021 to 28 December 2021), there were 1132 case reports (798 initial reports [670 concerning Dose 1 and 127 concerning Dose 2 and 1 case concerning dose 3]. There was one case (PPD , from PPD received via PPD) reported with Dose 3, the vaccinee experienced “sepsis chest secondary to blood clot on lungs” on the same day of vaccination. However, upon review this was considered a coding

issue and there was no evidence of concurrent thrombocytopenia in this case. There were 334 follow-up reports [321 concerning Dose 1 and 13 concerning Dose 2]). Further analysis in this report is focused on the cumulative report.

Of these 2059 case reports, 1072 (52%) reports were reported in females, 929 (45%) reports in males, and in 58 (3%) cases the gender was not reported.

Seven hundred and forty-two (742 [36%]) originated from UK and the other cases (≥10) were from the following countries: Australia (373), Germany (242), Italy (101), Brazil (73), Canada (69), France (59), Spain (54), Netherlands (49), Belgium (42), India (27), Sweden (22), Austria (21), Poland (17), Finland (15), Greece (15) and Norway (14).

Seven percent (151) of the cases were reported for vaccinees aged 18-29 years; 10% (211) in vaccinees aged 30-39 years, 16% (329) in vaccinees aged 40-49 years; 19% (377) in vaccinees aged 50-59 years, 21% (436) in vaccinees aged 60-69 years, 14% (271) in vaccinees aged 70-79 years, 5% (112) in vaccinees aged ≥ 80 years, and in 8% (172) vaccinees age was unknown. The age range was 18 – 104 years with a median of 56 years.

Seventeen percent (348/2059) of the cases reported fatal outcome compared to the 18% (245/1375) fatal outcome reported in the previous PBRER report and October-November, August-September, July, June, May, April, and March SSRs with rates of 17% (332/1987), 17% (310/1809), 18% (267/1503), 18% (245/1375), 19% (210/1095), 22% (150/679) and 27% (49 out of 184), respectively. Fatality/survival rate cumulatively for each month up to 28 December 2021 is presented in Table 142 and Figure 2.

Case level outcome in remaining cases were Not recovered (698), Recovered (208), Recovered with sequelae (36), Recovering (425), and Unknown (345). Time to onset (TTO) to TTS event was available in 1636 (79%) case reports and ranged from 0 day to 226 days; median time to onset (TTO) was 12 days. TTO for events within 14, 21 and 42 days by Dose 1, Dose 2 and fatal reports are presented in Table 130. Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-three percent of the fatal report occurred with 14 days compare to 64% for all cases and 88% of the fatal report occurred with 21 days compare to 80% for all cases.

Table 130 Time to onset for thrombosis in combination with thrombocytopenia cases

Row Labels	All cases N (%)	Dose 1 N (%)	Dose 2 N (%)	Fatal reports N (%)
Time to onset available	1636 (79)	1445 (78)	190 (90)	268 (77)
0 to 14 days	1042 (64)	931 (64)	110 (58)	196 (73)
0 to 21 days	1315 (80)	1179 (82)	135 (71)	236 (88)

Table 130 Time to onset for thrombosis in combination with thrombocytopenia cases

Row Labels	All cases N (%)	Dose 1 N (%)	Dose 2 N (%)	Fatal reports N (%)
0 to 42 days	1534 (94)	1361 (94)	172 (91)	257 (96)

N Number.

Of the 2059 case reports, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 522 (25%) cases. Of the 2059 case reports, 113 (5%) had the co-reported events from the HLT: Coagulopathies (including 60 cases with DIC) and 801 (39%) case reports had co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms).

The most common (≥10) bleeding events included Immune thrombocytopenia (254), Cerebral haemorrhage (194), Haemorrhage (66), Subarachnoid haemorrhage (60), Haemorrhage intracranial (59), Contusion (53), Petechiae (46), Thrombotic thrombocytopenic purpura (39), Haemoptysis (24), Cerebral haematoma (21), Haematoma (21), Haemorrhagic stroke (19), Adrenal haemorrhage (15), Haemorrhagic transformation stroke (15), Rectal haemorrhage (13), Epistaxis (12), Haematuria (10) and Haemorrhagic cerebral infarction (10).

A total of 309 case reports contained PTs from the SMQ: Embolic and thrombotic events, arterial; 1460 reports contained PTs from the SMQ: Embolic and thrombotic events, venous; and 880 reports contained PTs from the SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. Thrombosis events by site and age group and gender is presented in Table 131. The Table 131 includes all events irrespective of Dose 1 or Dose 2. One case may contain >1 reported thrombosis event; hence the event count is more than the case count. There are 412 events in 309 case reports for SMQ: Embolic and thrombotic events, arterial. The most common (≥30) arterial Embolic and thrombotic events included Aortic thrombosis, Ischaemic stroke, Peripheral artery thrombosis and Thrombotic thrombocytopenic purpura. There are 1163 events in 880 case reports for SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. This included most common events (>30) Cerebral infraction, Cerebral thrombosis, Cerebrovascular accident, Disseminated intravascular coagulation, Embolism, Hemiparesis, Hemiplegia, Heparin-induced thrombocytopenia, Thrombosis and Thrombosis with thrombocytopenia syndrome. There are 2157 events in 1460 case reports for SMQ: Embolic and thrombotic events, venous. The most common (≥30) venous Embolic and thrombotic events included Cerebral venous sinus thrombosis, Cerebral venous thrombosis, Deep vein thrombosis, Hepatic vein thrombosis, Jugular vein thrombosis, Mesenteric vein thrombosis, Portal vein thrombosis, Pulmonary embolism, splenic vein thrombosis, venous thrombosis and Superior sagittal sinus

thrombosis. Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism and Thrombosis.

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Arterial																						
Acute myocardial infarction		1		1	1	1	4		2	5		2	2		3	3						25
Aortic embolus				1						2		2	1		2				1			9
Aortic thrombosis				2	1	5	2		4	5		5	7		3	1		1	1			37
Arterial occlusive disease												1			1							2
Arterial thrombosis	1			2	1	2	1		2	2	1	4	6		2			1	1			26
Carotid artery occlusion				1		1	1					2				1						6
Carotid artery thrombosis	1	3		3	6	1	2		3	1		4	2						2			28
Cerebral artery embolism	1														1							2
Cerebral artery occlusion									3			2			1							6
Cerebral artery thrombosis				1			4		6	2		1	1			1			1			17
Cerebrovascular insufficiency					1																	1
Coronary artery bypass				1																		1
Coronary artery occlusion										1												1
Coronary artery thrombosis				1		1	3		3	2						1						11
Embolism arterial							2		1			2										5

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Femoral artery embolism												1										1
Hepatic artery thrombosis						1						1							1			3
Iliac artery occlusion													1									1
Internal capsule infarction															1							1
Ischaemic cerebral infarction						2				3		1	1									7
Ischaemic stroke	1	2		6	2	3	1		10	2		4	5		4		1	1	1			43
Lacunar infarction					1					1			1					1				4
Mesenteric artery thrombosis		1										2								1		4
Myocardial infarction	1			1			4		2	3		2	6		2	4						25
Peripheral arterial occlusive disease										1					1				1			3
Peripheral artery occlusion							1		1	1		3	2		2							10
Peripheral artery thrombosis				2	1	2	6		4	6		9	2		3	2			1			38
Peripheral embolism	1	1					1			2		1	1									7
Pulmonary artery occlusion							1					1										2

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Pulmonary artery thrombosis							1		3	1		2	1									8
Renal artery occlusion													1									1
Renal artery thrombosis										1			1			1						3
Renal embolism												1										1
Retinal artery occlusion				1			1															2
Splenic artery thrombosis	PPD																					6
Stress cardiomyopathy																						1
Subclavian artery thrombosis						1																1
Thromboembolectomy												1										1
Thrombotic microangiopathy												3							1			4
Thrombotic thrombocytopenic purpura	2			2	1	5	2		2	5		5	1		2	3	2	1	4	1	1	39
Transient ischaemic attack					1	2				1			7			4		1		1		17
Truncus coeliacus thrombosis															1							1
Vertebral artery thrombosis						1																1
Arterial Total	**8**	**8**	**0**	**26**	**16**	**29**	**38**	**0**	**47**	**47**	**1**	**63**	**50**	**0**	**29**	**22**	**3**	**6**	**15**	**3**	**1**	**412**

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Mixed																						
Adrenal thrombosis					1	1																2
Antiphospholipid syndrome						1				1		1			1				1			5
Atrial thrombosis												2	1			1				1		5
Autoimmune heparin-induced thrombocytopenia	PPD																					1
Brain stem infarction																						1
Brain stem stroke															1							1
Cardiac ventricular thrombosis							1			1		1	1		1	1		1		2		9
Cerebellar infarction	PPD																					3
Cerebral congestion									1													1
Cerebral infarction	PPD																					55
Cerebral ischaemia						1			1	1			2									5
Cerebral thrombosis	4	5		4	4	6			10	4		2	2			2	3		2			48
Cerebrovascular accident	2	1		7	2	10	6		5	2		11	4		4	8	7	3	3	4	2	81
Disseminated intravascular coagulation	2	5		5	2	4	3		5	2		7	4		12	2	1		3		1	58
Embolic cerebral infarction												1	1									2
Embolic stroke												1					1					2

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Embolism	2	1		5	2	7	5		4	7		3	6		5	5	1	3	3	4		63
Foetal vascular malperfusion	PPD																					1
Haemorrhagic adrenal infarction				1	1					1		1				1	1					6
Haemorrhagic cerebral infarction	PPD																					10
Haemorrhagic infarction	2	1		4								1	1									9
Haemorrhagic stroke		2		3		2	1		3	1		5	1			1						19
Haemorrhagic transformation stroke				2	1	2	1					3	2		1		2		1			15
Haemorrhoids thrombosed						1																1
Hemiparesis	PPD																					79
Hemiplegia																						32
Heparin-induced thrombocytopenia	2	1		3	4	5	4			4		2	6		3	1	1	1	1		1	39
Hepatic infarction							1			1		2			1							5
Hepatic vascular thrombosis				1		2	1						1			1					1	7
Infarction				2		1			3			1	1					1				9
Intestinal infarction				3		1	1		1	1		1										8
Intracardiac thrombus							4		1	1					2			1				9

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Mesenteric vascular occlusion				1																		1
Monoparesis	PPD																					4
Monoplegia																						2
Pancreatic infarction													1									1
Paraparesis	PPD																					1
Post procedural stroke										1												1
Prosthetic cardiac valve thrombosis																1						1
Quadriparesis	PPD																					3
Quadriplegia																						2
Renal infarct				3		2	2			3			3					1				14
Renal vascular thrombosis					1	1	1		1													4
Splenic infarction				3		1	2		3	2		4	2		2			1				20
Splenic thrombosis						1	3		1	1												6
Thalamic infarction	PPD																					1
Thrombectomy									1											1		2
Thrombosis	12	3	1	20	21	37	32		35	36		37	33	1	18	27	5	8	24	11	37	398
Thrombosis in device													1									1

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Thrombosis mesenteric vessel				1		2	3		1	1												8
Thrombosis with thrombocytopenia syndrome	6	2		10	3	9	8		5	3		12	9	1	1	7	1	3	4	3	5	92
Thrombotic stroke						2				1					2							5
Vascular graft thrombosis													1									1
Vascular operation																				1		1
Vascular stent thrombosis				1									1			1						3
Mixed Total	**47**	**32**	**1**	**92**	**55**	**122**	**93**	**0**	**105**	**94**	**0**	**123**	**96**	**2**	**62**	**62**	**27**	**27**	**45**	**31**	**47**	**1163**
Venous																						
Axillary vein thrombosis													1									1
Budd-Chiari syndrome						2																2
Cavernous sinus thrombosis	2					1			1				1						1			6
Cerebral venous sinus thrombosis	21	29		39	26	71	24		47	28		46	18		5	3	1	4	11	6	3	382
Cerebral venous thrombosis	9	9		10	7	18	8		9	6		13	6		2	1				5	1	104
Deep vein thrombosis	7	4		6	10	10	18		30	31	2	45	67		28	49	17	20	6	9		359

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Embolism venous	1								1	1		1	2									6
Hepatic vein embolism									1													1
Hepatic vein occlusion					1																	1
Hepatic vein thrombosis	3	1		2		3	3		5			7	4		2	1			1	1		33
Jugular vein occlusion						1							2									3
Jugular vein thrombosis	3	2		2	2	10	4		5	3		7	1		1	1			2			43
Mesenteric vein thrombosis		1		7	2	6	4		8	3		2	3		4	1	1	1	1	1		45
Ophthalmic vein thrombosis	1								4				1					1				7
Ovarian vein thrombosis				1		1			1						1							4
Pelvic venous thrombosis	1			4	1	2	1		2	5		5				1			1			23
Peripheral vein occlusion										1												1
Portal vein cavernous transformation																1						1
Portal vein embolism						1																1
Portal vein occlusion						2	1															3
Portal vein thrombosis	9	6		18	11	18	9	1	26	17		11	9		6	3	3	1	2	1		151
Portosplenomesenteric venous thrombosis				1	1		1		2	2		2	1								1	11
Post thrombotic syndrome															1							1

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Pulmonary embolism	26	10		26	16	39	41	2	64	44		75	99		45	76	26	29	17	21	1	657
Pulmonary infarction						1	2		8	1		1			1		1			1		16
Pulmonary thrombosis	1			1	1	2	1		1	2		1	3			1				1	1	16
Pulmonary venous thrombosis												2										2
Renal vein embolism		1																				1
Renal vein thrombosis	1	1		3		4			2			3	1		2							17
Retinal vein occlusion		1										3	1			1						6
Retinal vein thrombosis												2							1			3
Splenic vein occlusion							1															1
Splenic vein thrombosis	2	1		9	3	4	1		6	2		4	3		2							37
Subclavian vein thrombosis																	1					1
Superficial vein thrombosis					1	5	2		5	3		2	4		1	2	1	2				28
Superior sagittal sinus thrombosis	7	5		6	3	9	5		6	4		2	3		1		1		1	1		54
Thrombophlebitis					1	1			3	5	1	2	2					1	1			17
Transverse sinus thrombosis		3		4		3	2		3	2		2	2		2							23
Vena cava filter insertion										1												1
Vena cava thrombosis									3				1			1						5

Table 131 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

	Age - 18-29 Yrs			Age - 30-39 Yrs		Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs		Age - 80+ Yrs		Age Unknown			Grand Total
PT/Gender	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**F**	**M**	**F**	**M**	**U**	
Venoocclusive liver disease						1																1
Venous occlusion										1												1
Venous thrombosis	2			4	6	3	6		6	2		5	1		3		1		1	2		42
Venous thrombosis limb				1		2			1	2		3	1									10
Visceral venous thrombosis	1			4		5	2		6	4		3	2		1	1						29
Venous Total	**97**	**74**	**0**	**148**	**92**	**225**	**136**	**3**	**256**	**170**	**3**	**249**	**239**	**0**	**108**	**143**	**53**	**59**	**46**	**49**	**7**	**2157**

F Female; M Male; PT Preferred Term; U Gender unknown

Reporting Rate and Observed versus Expected Analysis

Reporting rate for thrombosis in combination with thrombocytopenia across all age groups based on the data from both UK and EEA by risk window of 21 days and 42 days is provided in Table 132 and Table 133 respectively. Reporting rate is also stratified by Dose 1 and Dose 2.

The overall TTS reporting rate from the UK was 10.4/million (508 identified reports with time to onset ≤ 21 days; estimated exposure 49.02 million administered doses) when compared to 5.6 (event rates per 1M Person Years (PY) per 21 days Truven Market Scan- 2019, aligned with the Observational Health Data Science and Informatics (OHDSI) TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan-2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable and possible) cases was 9.02/million administered doses. Reporting rate for Dose 1 and Dose 2 was 17.54 and 2.98/million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in 18-39 and 40-49 age group was higher when compared to background rate; however reporting rate in 50-64 and 65+ age group was less compared to the background rate. Reporting rate for Dose 2 was within the background rate for overall and all age stratifications.

The overall TTS reporting rate from the EEA was 11.45 /million (522 identified reports with time to onset ≤ 21 days; estimated exposure 45.58 million administered doses) when compared to 5.6 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan- 2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable and possible) was 5.66/million administered doses. Reporting rate for Dose 1 and Dose 2 was 20.98 and 0.92/million doses administered doses. EEA Reporting rate in 18-49 age group and 50-59 years age group with all doses and Dose 1 was higher when compared to background rate; reporting rate for Dose 2 was within the background rate for overall and all age stratifications.

The reporting rate for cases occurring within 42 days from UK and EEA are provided in Table 133. About 95% of the cases have occurred within 42 days after vaccination.

Table 132 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All doses (UK)								
Age - 18-39 Yrs	6005301	90	80	14.99	13.32	2.1-3.2	12.89 to 11.79	11.22 to 10.12
Age - 40-49 Yrs	10195312	132	109	12.95	10.69	3.4-6.3	9.55 to 6.65	7.29 to 4.39
Age - 50-64 Yrs	18891602	156	141	8.26	7.46	7.3-14.9	0.96 to -6.64	0.16 to -7.44
Age - > 65 Yrs	13760415	99	86	7.19	6.25	23.4-44.4	-16.21 to -37.21	-17.15 to -38.15
Age Unknown	167800	31	27	184.74	160.91	-	-	-
Grand Total	49020430	508	442	10.36	9.04	5.6-10.7	4.76 to -0.34	3.44 to -1.66
Dose 1 (UK)								
Age - 18-39 Yrs	3067234	87	77	28.36	25.1	2.1-3.2	26.26 to 25.16	23 to 21.9
Age - 40-49 Yrs	5170940	126	104	24.37	20.11	3.4-6.3	20.97 to 18.07	16.71 to 13.81
Age - 50-64 Yrs	9521965	139	128	14.6	13.44	7.3-14.9	7.3 to -0.3	6.14 to -1.46
Age - > 65 Yrs	6932257	59	52	8.51	7.5	23.4-44.4	-14.89 to -35.89	-15.9 to -36.9
Age Unknown	111055	24	20	216.11	180.09	-	-	-
Grand Total	24803451	435	381	17.54	15.36	5.6-10.7	11.94 to 6.84	9.76 to 4.66
Dose 2 (UK)								

Table 132 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - 18-39 Yrs	2933789	3	3	1.02	1.02	2.1-3.2	-1.08 to -2.18	-1.08 to -2.18
Age - 40-49 Yrs	5018787	6	5	1.2	1	3.4-6.3	-2.2 to -5.1	-2.4 to -5.3
Age - 50-64 Yrs	9354376	17	13	1.82	1.39	7.3-14.9	-5.48 to -13.08	-5.91 to -13.51
Age - > 65 Yrs	6804552	39	34	5.73	5	23.4-44.4	-17.67 to -38.67	-18.4 to -39.4
Age Unknown	56622	7	7	123.63	123.63	-	-	-
Grand Total	24168126	72	62	2.98	2.57	5.6-10.7	-2.62 to -7.72	-3.03 to -8.13
All doses (EEA)								
18-49	11513485	190	103	16.5	8.95	2.61-4.34	12.16 to 13.89	4.61 to 6.34
50-59	6275981	97	55	15.46	8.76	5.98-12.3	3.16 to 9.48	-3.54 to 2.78
60-69	18684704	157	78	8.4	4.17	11-22.5	-14.1 to -2.6	-18.33 to -6.83
70-79	8010180	53	15	6.62	1.87	22.3-45.2	-38.58 to -15.68	-43.33 to -20.43
80+	1094043	12	4	10.97	3.66	34.2-55.9	-44.93 to -23.23	-52.24 to -30.54
Age Unknown	7637	13	3	1702.24	392.82	-	-	-
Grand Total	45586030	522	258	11.45	5.66	5.62-10.7	0.75 to 5.83	-5.04 to 0.04
Dose 1 (EEA)								
18-49	6274541	186	101	29.64	16.1	2.61-4.34	25.3 to 27.03	11.76 to 13.49
50-59	3406841	95	55	27.89	16.14	5.98-12.3	15.59 to 21.91	3.84 to 10.16
60-69	9600344	148	76	15.42	7.92	11-22.5	-7.08 to 4.42	-14.58 to -3.08

Table 132 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
70-79	4084682	48	13	11.75	3.18	22.3-45.2	-33.45 to -10.55	-42.02 to -19.12
80+	559647	12	4	21.44	7.15	34.2-55.9	-34.46 to -12.76	-48.75 to -27.05
Age Unknown	3956	13	3	3286.15	758.34	-	-	-
Grand Total	23930011	502	252	20.98	10.53	5.62-10.7	10.28 to 15.36	-0.17 to 4.91
Dose 2 (EEA)								
18-49	5236563	4	2	0.76	0.38	2.61-4.34	-3.58 to -1.85	-3.96 to -2.23
50-59	2867674	2	0	0.7	0	5.98-12.3	-11.6 to -5.28	-12.3 to -5.98
60-69	9082233	9	2	0.99	0.22	11-22.5	-21.51 to -10.01	-22.28 to -10.78
70-79	3923679	5	2	1.27	0.51	22.3-45.2	-43.93 to -21.03	-44.69 to -21.79
80+	533368	0	0	0	0	34.2-55.9	-55.9 to -34.2	-55.9 to -34.2
Age Unknown	3681	0	0	0	0	-	-	-
Grand Total	**21647198**	**20**	**6**	**0.92**	**0.28**	**5.62-10.7**	**-9.78 to -4.7**	**-10.42 to -5.34**

[a] Background event rates per 1M PY per 21 days from Truven Market Scan-2019

EEA European Economic Area; UK United Kingdom.

Table 133 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All doses (UK)								
Age - 18-39 Yrs	6005301	100	87	16.65	14.49	4.2-6.4	12.45 to 10.25	10.29 to 8.09
Age - 40-49 Yrs	10195312	145	119	14.22	11.67	6.8-12.6	7.42 to 1.62	4.87 to -0.93
Age - 50-64 Yrs	18891602	187	170	9.9	9	14.6-29.8	-4.7 to -19.9	-5.6 to -20.8
Age - > 65 Yrs	13760415	128	110	9.3	7.99	46.8-88.8	-37.5 to -79.5	-38.81 to -80.81
Age Unknown	167800	39	33	232.42	196.66	-	-	-
Grand Total	49020430	599	519	12.22	10.59	11.2-21.4	1.02 to -9.18	-0.61 to -10.81
Dose 1 (UK)								
Age - 18-39 Yrs	3067234	96	84	31.3	27.39	4.2-6.4	27.1 to 24.9	23.19 to 20.99
Age - 40-49 Yrs	5170940	138	113	26.69	21.85	6.8-12.6	19.89 to 14.09	15.05 to 9.25
Age - 50-64 Yrs	9521965	167	154	17.54	16.17	14.6-29.8	2.94 to -12.26	1.57 to -13.63
Age - > 65 Yrs	6932257	80	68	11.54	9.81	46.8-88.8	-35.26 to -77.26	-36.99 to -78.99
Age Unknown	111055	28	23	252.13	207.1	-	-	-

Table 133 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Grand Total	24803451	509	442	20.52	17.82	11.2-21.4	9.32 to -0.87	6.62 to -3.58
Dose 2 (UK)								
Age - 18-39 Yrs	2933789	4	3	1.36	1.02	4.2-6.4	-2.84 to -5.04	-3.18 to -5.38
Age - 40-49 Yrs	5018787	7	6	1.39	1.2	6.8-12.6	-5.41 to -11.21	-5.6 to -11.4
Age - 50-64 Yrs	9354376	20	16	2.14	1.71	14.6-29.8	-12.46 to -27.66	-12.89 to -28.09
Age - > 65 Yrs	6804552	47	42	6.91	6.17	46.8-88.8	-39.89 to -81.89	-40.63 to -82.63
Age Unknown	56622	11	10	194.27	176.61	-	-	-
Grand Total	24168126	89	77	3.68	3.19	11.2-21.4	-7.52 to -17.72	-8.01 to -18.21
All doses (EEA)								
18-49	11513485	207	107	17.98	9.29	5.22-8.68	9.3 to 12.76	0.61 to 4.07
50-59	6275981	106	59	16.89	9.4	11.96-24.6	-7.71 to 4.93	-15.2 to -2.56
60-69	18684704	181	87	9.69	4.66	22-45	-35.31 to -12.31	-40.34 to -17.34
70-79	8010180	63	17	7.86	2.12	44.6-90.4	-82.54 to -36.74	-88.28 to -42.48
80+	1094043	15	6	13.71	5.48	68.4-111.8	-98.09 to -54.69	-106.32 to -62.92

Table 133 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	7637	14	3	1833.18	392.82	-	-	-
Grand Total	45586030	586	279	12.85	6.12	11.24-21.4	-8.55 to 1.61	-15.28 to -5.12
Dose 1 (EEA)								
18-49	6274541	203	105	32.35	16.73	5.22-8.68	23.67 to 27.13	8.05 to 11.51
50-59	3406841	104	59	30.53	17.32	11.96-24.6	5.93 to 18.57	-7.28 to 5.36
60-69	9600344	167	84	17.4	8.75	22-45	-27.6 to -4.6	-36.25 to -13.25
70-79	4084682	58	15	14.2	3.67	44.6-90.4	-76.2 to -30.4	-86.73 to -40.93
80+	559647	15	6	26.8	10.72	68.4-111.8	-85 to -41.6	-101.08 to -57.68
Age Unknown	3956	14	3	3538.93	758.34	-	-	-
Grand Total	23930011	561	272	23.44	11.37	11.24-21.4	2.04 to 12.2	-10.03 to 0.13
Dose 2 (EEA)								
18-49	5236563	4	2	0.76	0.38	5.22-8.68	-7.92 to -4.46	-8.3 to -4.84
50-59	2867674	2	0	0.7	0	11.96-24.6	-23.9 to -11.26	-24.6 to -11.96
60-69	9082233	14	3	1.54	0.33	22-45	-43.46 to -20.46	-44.67 to -21.67
70-79	3923679	5	2	1.27	0.51	44.6-90.4	-89.13 to -43.33	-89.89 to -44.09

Table 133 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
80+	533368	0	0	0	0	68.4-111.8	-111.8 to -68.4	-111.8 to -68.4
Age Unknown	3681	0	0	0	0	-	-	-
Grand Total	21647198	25	7	1.15	0.32	11.24-21.4	-20.25 to -10.09	-21.08 to -10.92

[a] Background event rates per 1M PY per 42 days from Truven Market Scan-2019

EEA European Economic Area; UK United Kingdom.

Observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented below (Table 134, Table 135 and Table 136). Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS. Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded).

The background rate (incidence rate) of TTS is 9.77 /100,000 person year and 11.14/100,000 person year. The observed number of cases, for all risk windows of 14, 21 and 42 days (with unknown time to onset not included) is less than expected post vaccination by COVID-19 VACCINE ASTRAZENECA.

The observed number of cases are significantly more than expected, for risk windows of 14 days (with unknown time to onset included) post vaccination by COVID-19 VACCINE ASTRAZENECA of TTS with both background rates.

The observed number of cases for risk windows of 21 days (with unknown time to onset included) post vaccination by COVID-19 VACCINE ASTRAZENECA of TTS is greater than the expected with background rate 9.77/100,000 person year and lesser than the expected with background rate with 11.14/100,000 person year.

The observed number of cases for risk windows of 42 days (with unknown time to onset included) post vaccination by COVID-19 VACCINE ASTRAZENECA of TTS is less than expected with both background rates.

Table 134 Observed versus Expected Analysis for TTS

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Overall (Global)	14	9.77[c]	291626957	1042	1092.12	0.95 (0.9 - 1.01)	Observed < expected
TTS Overall (Global)	21	9.77[c]	291626957	1315	1638.17	0.8 (0.76 - 0.85)	Observed significantly < expected
TTS Overall (Global)	42	9.77[c]	291626957	1534	3276.35	0.47 (0.45 - 0.49)	Observed significantly < expected
TTS Overall (Global) (including cases with unknown TTO)	14	9.77[c]	291626957	1466	1092.12	1.34 (1.27 - 1.41)	Observed significantly > expected
TTS Overall (Global) (including cases with unknown TTO)	21	9.77[c]	291626957	1739	1638.17	1.06 (1.01 - 1.11)	Observed significantly > expected
TTS Overall (Global) (including cases with unknown TTO)	42	9.77[c]	291626957	1958	3276.35	0.6 (0.57 - 0.62)	Observed significantly < expected
TTS Overall (Global)	14	11.14[d]	291626957	1042	1245.26	0.84 (0.79 - 0.89)	Observed significantly < expected
TTS Overall (Global)	21	11.14[d]	291626957	1315	1867.89	0.7 (0.67 - 0.74)	Observed significantly < expected
TTS Overall (Global)	42	11.14[d]	291626957	1534	3735.78	0.41 (0.39 - 0.43)	Observed significantly < expected

Table 134 Observed versus Expected Analysis for TTS

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Overall (Global) (including cases with unknown TTO)	14	11.14[d]	291626957	1466	1245.26	1.18 (1.12 - 1.24)	Observed significantly > expected
TTS Overall (Global) (including cases with unknown TTO)	21	11.14[d]	291626957	1739	1867.89	0.93 (0.89 - 0.98)	Observed significantly < expected
TTS Overall (Global) (including cases with unknown TTO)	42	11.14[d]	291626957	1958	3735.78	0.52 (0.5 - 0.55)	Observed significantly < expected

[a] Incidence Rate 9.77/100,000 PY from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm.

TTS Thrombosis with Thrombocytopenia Syndrome

Table 135 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS 18 to 49	14	4.53	27716022	349	48.13	7.25 (6.51 - 8.05)	Observed significantly > expected
TTS 50 to 59	14	10.4	19552392	162	77.94	2.08 (1.77 - 2.42)	Observed significantly > expected

Table 135 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS 60 to 69	14	19.19	28510714	172	209.72	0.82 (0.7 - 0.95)	Observed significantly < expected
TTS 70 to 79	14	38.93	14795684	76	220.78	0.34 (0.27 - 0.43)	Observed significantly < expected
TTS over 80	14	59.54	3858135	20	88.05	0.23 (0.14 - 0.35)	Observed significantly < expected
TTS 18 to 49	21	4.53	27716022	412	72.19	5.71 (5.17 - 6.29)	Observed significantly > expected
TTS 50 to 59	21	10.4	19552392	215	116.92	1.84 (1.6 - 2.1)	Observed significantly > expected
TTS 60 to 69	21	19.19	28510714	227	314.57	0.72 (0.63 - 0.82)	Observed significantly < expected
TTS 70 to 79	21	38.93	14795684	105	331.17	0.32 (0.26 - 0.38)	Observed significantly < expected
TTS over 80	21	59.54	3858135	27	132.08	0.2 (0.13 - 0.3)	Observed significantly < expected

Table 135 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS 18 to 49	42	4.53	27716022	452	144.38	3.13 (2.85 - 3.43)	Observed significantly > expected
TTS 50 to 59	42	10.4	19552392	246	233.83	1.05 (0.92 - 1.19)	Observed > expected
TTS 60 to 69	42	19.19	28510714	269	629.15	0.43 (0.38 - 0.48)	Observed significantly < expected
TTS 70 to 79	42	38.93	14795684	129	662.35	0.19 (0.16 - 0.23)	Observed significantly < expected
TTS over 80	42	59.54	3858135	36	264.15	0.14 (0.1 - 0.19)	Observed significantly < expected
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods							
TTS 18 to 49	14	4.99	27716022	349	53.01	6.58 (5.91 - 7.31)	Observed significantly > expected
TTS 50 to 59	14	12.6	19552392	162	94.43	1.72 (1.46 - 2)	Observed significantly > expected
TTS 60 to 69	14	22.33	28510714	172	244.03	0.7 (0.6 - 0.82)	Observed significantly < expected

Table 135 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS 70 to 79	14	44.66	14795684	76	253.28	0.3 (0.24 - 0.38)	Observed significantly < expected
TTS over 80	14	58.18	3858135	20	86.04	0.23 (0.14 - 0.36)	Observed significantly < expected
TTS 18 to 49	21	4.99	27716022	412	79.52	5.18 (4.69 - 5.71)	Observed significantly > expected
TTS 50 to 59	21	12.6	19552392	215	141.65	1.52 (1.32 - 1.73)	Observed significantly > expected
TTS 60 to 69	21	22.33	28510714	227	366.05	0.62 (0.54 - 0.71)	Observed significantly < expected
TTS 70 to 79	21	44.66	14795684	105	379.92	0.28 (0.23 - 0.33)	Observed significantly < expected
TTS over 80	21	58.18	3858135	27	129.06	0.21 (0.14 - 0.3)	Observed significantly < expected
TTS 18 to 49	42	4.99	27716022	452	159.04	2.84 (2.59 - 3.12)	Observed significantly > expected

Table 135 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window	Background rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS 50 to 59	42	12.6	19552392	246	283.29	0.87 (0.76 - 0.98)	Observed significantly < expected
TTS 60 to 69	42	22.33	28510714	269	732.09	0.37 (0.32 - 0.41)	Observed significantly < expected
TTS 70 to 79	42	44.66	14795684	129	759.84	0.17 (0.14 - 0.2)	Observed significantly < expected
TTS over 80	42	58.18	3858135	36	258.12	0.14 (0.1 - 0.19)	Observed significantly < expected

[a] Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods
CI Confidence Interval; E Expected; EU European Union; O Observed; TTS Thrombosis with Thrombocytopenia Syndrome; UK United Kingdom

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS Female	14	9.22	24872206	203	87.9	2.31 (2 - 2.65)	Observed significantly > expected
TTS Male	14	13.24	23980140	179	121.7	1.47 (1.26 - 1.7)	Observed significantly > expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 18 to 49	14	4.64	8409902	102	14.96	6.82 (5.56 - 8.28)	Observed significantly > expected
TTS Female 50 to 59	14	10.71	6319086	37	25.94	1.43 (1 - 1.97)	Observed significantly > expected
TTS Female 60 to 69	14	15.87	4859019	28	29.56	0.95 (0.63 - 1.37)	Observed < expected
TTS Female 70 to 79	14	36.7	3562147	17	50.11	0.34 (0.2 - 0.54)	Observed significantly < expected
TTS Female over 80	14	39.61	1721795	7	26.14	0.27 (0.11 - 0.55)	Observed significantly < expected
TTS Male 18 to 49	14	5.36	7790110	75	16	4.69 (3.69 - 5.88)	Observed significantly > expected
TTS Male 50 to 59	14	14.7	6957211	47	39.2	1.2 (0.88 - 1.59)	Observed > expected
TTS Male 60 to 69	14	29.51	4966917	21	56.18	0.37 (0.23 - 0.57)	Observed significantly < expected
TTS Male 70 to 79	14	54.04	3223317	20	66.77	0.3 (0.18 - 0.46)	Observed significantly < expected
TTS Male over 80	14	84.62	1042292	7	33.81	0.21 (0.08 - 0.43)	Observed significantly < expected
TTS Female	21	9.22	24872206	266	131.85	2.02 (1.78 - 2.28)	Observed significantly > expected
TTS Male	21	13.24	23980140	237	182.55	1.3 (1.14 - 1.47)	Observed significantly > expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 18 to 49	21	4.64	8409902	125	22.44	5.57 (4.64 - 6.64)	Observed significantly > expected
TTS Female 50 to 59	21	10.71	6319086	54	38.91	1.39 (1.04 - 1.81)	Observed significantly > expected
TTS Female 60 to 69	21	15.87	4859019	37	44.34	0.83 (0.59 - 1.15)	Observed < expected
TTS Female 70 to 79	21	36.7	3562147	27	75.17	0.36 (0.24 - 0.52)	Observed significantly < expected
TTS Female over 80	21	39.61	1721795	7	39.21	0.18 (0.07 - 0.37)	Observed significantly < expected
TTS Male 18 to 49	21	5.36	7790110	94	24.01	3.92 (3.16 - 4.79)	Observed significantly > expected
TTS Male 50 to 59	21	14.7	6957211	63	58.8	1.07 (0.82 - 1.37)	Observed > expected
TTS Male 60 to 69	21	29.51	4966917	33	84.27	0.39 (0.27 - 0.55)	Observed significantly < expected
TTS Male 70 to 79	21	54.04	3223317	25	100.15	0.25 (0.16 - 0.37)	Observed significantly < expected
TTS Male over 80	21	84.62	1042292	8	50.71	0.16 (0.07 - 0.31)	Observed significantly < expected
TTS Female	42	9.22	24872206	307	263.7	1.16 (1.04 - 1.3)	Observed significantly > expected
TTS Male	42	13.24	23980140	287	365.1	0.79 (0.7 - 0.88)	Observed significantly < expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 18 to 49	42	4.64	8409902	139	44.87	3.1 (2.6 - 3.66)	Observed significantly > expected
TTS Female 50 to 59	42	10.71	6319086	63	77.82	0.81 (0.62 - 1.04)	Observed < expected
TTS Female 60 to 69	42	15.87	4859019	43	88.67	0.48 (0.35 - 0.65)	Observed significantly < expected
TTS Female 70 to 79	42	36.7	3562147	33	150.33	0.22 (0.15 - 0.31)	Observed significantly < expected
TTS Female over 80	42	39.61	1721795	10	78.42	0.13 (0.06 - 0.23)	Observed significantly < expected
TTS Male 18 to 49	42	5.36	7790110	103	48.01	2.15 (1.75 - 2.6)	Observed significantly > expected
TTS Male 50 to 59	42	14.7	6957211	76	117.6	0.65 (0.51 - 0.81)	Observed significantly < expected
TTS Male 60 to 69	42	29.51	4966917	45	168.55	0.27 (0.19 - 0.36)	Observed significantly < expected
TTS Male 70 to 79	42	54.04	3223317	33	200.3	0.16 (0.11 - 0.23)	Observed significantly < expected
TTS Male over 80	42	84.62	1042292	11	101.42	0.11 (0.05 - 0.19)	Observed significantly < expected
TTS Female							
TTS Male	14	13.24	23980140	179	121.7	1.47 (1.26 - 1.7)	Observed significantly > expected
TTS Female 18 to 49	14	4.64	8409902	102	14.96	6.82 (5.56 - 8.28)	Observed significantly > expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 50 to 59	14	10.71	6319086	37	25.94	1.43 (1 - 1.97)	Observed significantly > expected
TTS Female 60 to 69	14	15.87	4859019	28	29.56	0.95 (0.63 - 1.37)	Observed < expected
TTS Female 70 to 79	14	36.7	3562147	17	50.11	0.34 (0.2 - 0.54)	Observed significantly < expected
TTS Female over 80	14	39.61	1721795	7	26.14	0.27 (0.11 - 0.55)	Observed significantly < expected
TTS Male 18 to 49	14	5.36	7790110	75	16	4.69 (3.69 - 5.88)	Observed significantly > expected
TTS Male 50 to 59	14	14.7	6957211	47	39.2	1.2 (0.88 - 1.59)	Observed > expected
TTS Male 60 to 69	14	29.51	4966917	21	56.18	0.37 (0.23 - 0.57)	Observed significantly < expected
TTS Male 70 to 79	14	54.04	3223317	20	66.77	0.3 (0.18 - 0.46)	Observed significantly < expected
TTS Male over 80	14	84.62	1042292	7	33.81	0.21 (0.08 - 0.43)	Observed significantly < expected
TTS Female	21	9.22	24872206	266	131.85	2.02 (1.78 - 2.28)	Observed significantly > expected
TTS Male	21	13.24	23980140	237	182.55	1.3 (1.14 - 1.47)	Observed significantly > expected
TTS Female 18 to 49	21	4.64	8409902	125	22.44	5.57 (4.64 - 6.64)	Observed significantly > expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 50 to 59	21	10.71	6319086	54	38.91	1.39 (1.04 - 1.81)	Observed significantly > expected
TTS Female 60 to 69	21	15.87	4859019	37	44.34	0.83 (0.59 - 1.15)	Observed < expected
TTS Female 70 to 79	21	36.7	3562147	27	75.17	0.36 (0.24 - 0.52)	Observed significantly < expected
TTS Female over 80	21	39.61	1721795	7	39.21	0.18 (0.07 - 0.37)	Observed significantly < expected
TTS Male 18 to 49	21	5.36	7790110	94	24.01	3.92 (3.16 - 4.79)	Observed significantly > expected
TTS Male 50 to 59	21	14.7	6957211	63	58.8	1.07 (0.82 - 1.37)	Observed > expected
TTS Male 60 to 69	21	29.51	4966917	33	84.27	0.39 (0.27 - 0.55)	Observed significantly < expected
TTS Male 70 to 79	21	54.04	3223317	25	100.15	0.25 (0.16 - 0.37)	Observed significantly < expected
TTS Male over 80	21	84.62	1042292	8	50.71	0.16 (0.07 - 0.31)	Observed significantly < expected
TTS Female	42	9.22	24872206	307	263.7	1.16 (1.04 - 1.3)	Observed significantly > expected
TTS Male	42	13.24	23980140	287	365.1	0.79 (0.7 - 0.88)	Observed significantly < expected
TTS Female 18 to 49	42	4.64	8409902	139	44.87	3.1 (2.6 - 3.66)	Observed significantly > expected

Table 136 Observed versus Expected Analysis for TTS by age group/sex (United Kingdom)

Adverse Events	Risk window [a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Female 50 to 59	42	10.71	6319086	63	77.82	0.81 (0.62 - 1.04)	Observed < expected
TTS Female 60 to 69	42	15.87	4859019	43	88.67	0.48 (0.35 - 0.65)	Observed significantly < expected
TTS Female 70 to 79	42	36.7	3562147	33	150.33	0.22 (0.15 - 0.31)	Observed significantly < expected
TTS Female over 80	42	39.61	1721795	10	78.42	0.13 (0.06 - 0.23)	Observed significantly < expected
TTS Male 18 to 49	42	5.36	7790110	103	48.01	2.15 (1.75 - 2.6)	Observed significantly > expected
TTS Male 50 to 59	42	14.7	6957211	76	117.6	0.65 (0.51 - 0.81)	Observed significantly < expected
TTS Male 60 to 69	42	29.51	4966917	45	168.55	0.27 (0.19 - 0.36)	Observed significantly < expected
TTS Male 70 to 79	42	54.04	3223317	33	200.3	0.16 (0.11 - 0.23)	Observed significantly < expected
TTS Male over 80	42	84.62	1042292	11	101.42	0.11 (0.05 - 0.19)	Observed significantly < expected
TTS Female	14	9.22	24872206	203	87.9	2.31 (2 - 2.65)	Observed significantly > expected

[a] Only cases observed within 0-14, 0-21, and 0-42 days were included; Risk Window: 14, 21, and 42 days

CI Confidence interval, E Expected; O Observed; OHDSI Observational Health Data Science and Informatics, TTS Thrombosis with thrombocytopenia syndrome

Anti-PF-4, D-Dimer, and platelet levels for Dose 1, Dose 2 and Fatal Reports

All 2059 case reports were reviewed to classify the cases based on the PTs and laboratory data, as per the Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia (Figure 1).

Figure 1 Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia

Confirmed	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL +	Anti-PF4 Abs
Probable	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL	
Possible	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not met	One or none of the criteria are met			

Information in case reports was limited, with missing laboratory data on platelet count, D-dimer level, and PF-4 antibodies and also in many case reports there were incomplete entries (units, date of test, and type of test) for platelet levels, D-dimer, and PF-4.

Information on platelet count were available in 1392 (68%) of 2059 case reports; platelet count was <150 x 10^9/L in 1345 of the 1392 reports and in 47 case reports platelet count was >150 x 10^9/L. Among these 1345 vaccinees with reported platelet count <150 x 10^9/L, 583 (43%) had a platelet count of <50 x 10^9/L; in 361 (27%) had a platelet count was between 50 to <100 x 10^9/L; and 322 (24%) had a platelet count between 100 to 150 x 10^9/L.79 (6%), the platelet count was reported as <150 x 10^9/L, however exact value was not provided.

In remaining 667 (32%) of the 2059 case reports information on platelet count was not available.

In 27 of the 2059 case reports there was no venous/arterial thrombosis reported. Of the 2059 case reports, PF-4 antibodies were positive in 509 (25%) reports, negative in 390 (19 %) reports, unknown or pending in 1160 (56%) case reports.

D-dimer levels were reported in 827 (40%) of the 2059 case reports, however, in many reports the units were not specified. In 180 (22%) D-dimer levels were < 4000 ng/mL and in 647 (78%) case reports D-dimer levels were > 4000 ng/mL. In 1232 (60%) case reports D dimer levels were not provided/reported.

Of the 2059 case reports reviewed, based on the above case classification criteria, there were 1331 cases which met the MHRA criteria of TTS (Confirmed, probable or possible). The total number of confirmed cases were 282 (14%), probable cases were 335 (16%), possible cases were 714 (35%), unlikely 1 (0.05%) and criteria not met cases were 727 (35%). Out of all cases (1331) which met the criteria, the confirmed cases (282) comprised 21% of the total cases. In all cases (1331) where the diagnostic criteria were met, 463 (35%) cases had confounding factors. Many of the cases had more than one confounding factor. The confounding factors associated were: Autoimmune disease (93) {ITP (44), autoimmune thyroiditis (6), psoriasis (4), antiphospholipid syndrome (4), Crohn's disease (3), myasthenia gravis (1), Inflammatory bowel disease (3), ulcerative colitis (2), ankylosing spondylitis (2), rheumatoid arthritis (4), Guillain-barre syndrome (4), sarcoidosis (2), systemic lupus erythematous (2), autoimmune hepatitis (2), vasculitis (1), multiple sclerosis (2), Hemolytic anemia (1), Polymyalgia rheumatica (3), Thalassemia minor (1) and Connective tissue disorder (2)}; Malignancy (58), {breast cancer (16), prostate cancer (2), malignant melanoma (3), brain cancer (1), thyroid cancer (1), non-Hodgkin's lymphoma (2), polycythemia vera (2), bladder cancer (1), pituitary tumor (1), lung cancer (5), metastatic cancer (2), tonsil cancer (1), ovarian cancer (1), pancreatic cancer (2), testicular cancer (2), Carcinoma endometrium Uterus (1), vulvar cancer (1), cervix carcinoma (1), renal cell carcinoma (1), chronic lymphocytic leukemia (1), glioblastoma (1), gliomas (1), leukemia (1), lymphoma (2), lymphoproliferative disease (1), metastatic neoplasm (1), myelodysplastic neoplasm (1), neoplasm (2), sarcoma (1)}; Past history of heparin (132) information on the dates of heparin administration was not available, Obesity (67), Past and current history of Contraceptive (44), Past history of thrombosis (57), HIT (20), Past history of frequent abortion (3), HIV infection (2), Chronic Hepatitis B (2), Liver disease (1), COVID-19 illness (21), Cardiomyopathy resulting from Fredrich's ataxia (1), Chronic kidney disease (1), Chronic glomerulonephritis (1), Dress syndrome (1), Liver transplant (1), Past history of stroke (1), Polycystic ovary syndrome (1), Protein C deficiency (2), Sickle cell disease (3), TCP chronic (1).Concomitant medications; Venaflaxine (3), and Citalopram and Clopidogrel combination (1).

In out of 282 confirmed reports, there were 123 (44%) cases with confounding factors. The confounding factor associated were; Past history of heparin (24), cancer (14) {Neoplasm (1), Abdominal neoplasm (1), Thyroid cancer (1), Prostate cancer (2), Vulvar cancer (1), Metastatic cancer (1), skin cancer (1), pancreatic cancer (1) Carcinoma endometrium Uterus (1), Non-Hodgkin's disease (1), breast cancer (3), malignant melanoma (1)}, Obesity (18), Contraceptives (19), ITP (14), Autoimmune disease (11) {Sarcoidosis (1), Guillain-Barre syndrome (1), Myasthenia gravis (1), Ankylosing Spondylitis (1), autoimmune thyroiditis (2),

antiphospholipid syndrome (1), ulcerative colitis (2), rheumatoid arthritis (1), Crohn's disease (1)}, HIT (6), Past history of thrombosis (17), Chronic kidney disease (1). The dates of heparin administered was not reported in all cases.

Demographics and clinical characteristics of thrombosis in combination of thrombocytopenia is provided in Table 137 and Table 138. Comparison of Platelet count, thrombosis event, PF-4 antibodies and D-dimer levels is provided in Table 139.

TTS case reports by age/gender, Dose, Case Classification, and fatality are presented in Table 140.

Based on the MHRA case classification criteria, 65% were categorised as confirmed/probable/possible (21% of the cases met confirmed criteria, 25% met probable criteria, 54% met possible criteria). The remaining 35% cases did not meet criteria and <1% of the cases were classified as unlikely. There was no difference in the case categorisation criteria between dose 1, 2 and fatal case reports. For the cases that occurred after the Dose 2, 74% were categorised as confirmed/probable/possible, (4% of the cases met confirmed criteria, 21% met probable criteria, 49% met possible criteria) and 26% were categorised as criteria not met.

Table 137 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed reports (n=282)	Probable Reports (n=336)	Possible Reports (n=714)	Unlikely Reports (n=1)	Criteria not met Reports (n=727)	All case reports (n=2059)
Median age in years (range)	47 (18-83)	55 (18-92)	60 (18-104)	65 (60-72)	58 (18-95)	56 (18-104)
Sex						
Female n (%)	157 (7.62)	180 (8.74)	367 (17.81)	0 (0)	368 (17.86)	1072 (52.06)
Male n (%)	124 (6.01)	151 (7.33)	344 (16.69)	1 (0.04)	309 (15)	929 (45.09)
Unknown n (%)	1 (0.04)	4 (0.19)	3 (0.14)	0 (0)	50 (2.42)	58 (2.81)
Region						
EEA						
Austria	3 (0.14)	6 (0.29)	5 (0.24)	0 (0)	7 (0.33)	21 (1.01)
Belgium	10 (0.48)	3 (0.14)	11 (0.53)	0 (0)	18 (0.87)	42 (2.03)
Bulgaria	0 (0)	0 (0)	1 (0.04)	0 (0)	3 (0.14)	4 (0.19)
Croatia	1 (0.04)	1 (0.04)	0 (0)	0 (0)	0 (0)	2 (0.09)
Cyprus	0 (0)	2 (0.09)	1 (0.04)	0 (0)	1 (0.04)	4 (0.19)

Table 137 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed reports (n=282)	Probable Reports (n=336)	Possible Reports (n=714)	Unlikely Reports (n=1)	Criteria not met Reports (n=727)	All case reports (n=2059)
Czech Republic	1 (0.04)	3 (0.14)	3 (0.14)	0 (0)	0 (0)	7 (0.33)
Denmark	1 (0.04)	0 (0)	0 (0)	0 (0)	3 (0.14)	4 (0.19)
Estonia	0 (0)	1 (0.04)	0 (0)	0 (0)	1 (0.04)	2 (0.09)
Finland	0 (0)	0 (0)	2 (0.09)	0 (0)	13 (0.63)	15 (0.72)
France	0 (0)	2 (0.09)	12 (0.58)	0 (0)	45 (2.18)	59 (2.86)
Germany	21 (1.01)	23 (1.11)	63 (3.05)	0 (0)	135 (6.55)	242 (11.74)
Greece	2 (0.09)	4 (0.19)	4 (0.19)	0 (0)	5 (0.24)	15 (0.72)
Hungary	0 (0)	0 (0)	2 (0.09)	0 (0)	2 (0.09)	4 (0.19)
Iceland	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.14)	3 (0.14)
Ireland	2 (0.09)	0 (0)	5 (0.24)	0 (0)	1 (0.04)	8 (0.38)
Italy	6 (0.29)	16 (0.77)	19 (0.92)	0 (0)	60 (2.91)	101 (4.9)
Latvia	0 (0)	1 (0.04)	1 (0.04)	0 (0)	0 (0)	2 (0.09)
Lithuania	0 (0)	0 (0)	2 (0.09)	0 (0)	0 (0)	2 (0.09)
Luxembourg	1 (0.04)	0 (0)	1 (0.04)	0 (0)	0 (0)	2 (0.09)
Malta	0 (0)	0 (0)	1 (0.04)	0 (0)	2 (0.09)	3 (0.14)
Netherlands	2 (0.09)	12 (0.58)	24 (1.16)	0 (0)	11 (0.53)	49 (2.37)
Norway	4 (0.19)	3 (0.14)	1 (0.04)	0 (0)	6 (0.29)	14 (0.67)
Poland	0 (0)	1 (0.04)	5 (0.24)	0 (0)	11 (0.53)	17 (0.82)
Portugal	0 (0)	2 (0.09)	2 (0.09)	0 (0)	4 (0.19)	8 (0.38)
Slovakia	0 (0)	0 (0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.09)
Slovenia	3 (0.14)	0 (0)	0 (0)	0 (0)	1 (0.04)	4 (0.19)
Spain	7 (0.33)	9 (0.43)	15 (0.72)	0 (0)	23 (1.11)	54 (2.62)
Sweden	0 (0)	0 (0)	3 (0.14)	0 (0)	19 (0.92)	22 (1.06)
United Kingdom	164 (7.96)	189 (9.17)	262 (12.71)	1 (0.04)	126 (6.11)	742 (36.01)
Rest of the world (ROW)						
Argentina	0 (0)	0 (0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.09)
Australia	22 (1.06)	34 (1.65)	205 (9.95)	0 (0)	112 (5.43)	373 (18.1)
Brazil	10 (0.48)	13 (0.63)	23 (1.11)	0 (0)	27 (1.31)	73 (3.54)
Canada	11 (0.53)	0 (0)	13 (0.63)	0 (0)	45 (2.18)	69 (3.34)
[redacted]	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)	1 (0.04)

Table 137 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed reports (n=282)	Probable Reports (n=336)	Possible Reports (n=714)	Unlikely Reports (n=1)	Criteria not met Reports (n=727)	All case reports (n=2059)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Egypt	0 (0)	0 (0)	1 (0.04)	0 (0)	2 (0.09)	3 (0.14)
India	2 (0.09)	3 (0.14)	11 (0.53)	0 (0)	10 (0.48)	26 (1.26)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Japan	1 (0.04)	1 (0.04)	0 (0)	0 (0)	0 (0)	2 (0.09)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Korea, Republic of	3 (0.14)	0 (0)	0 (0)	0 (0)	5 (0.24)	8 (0.38)
[redacted]	0 (0)	0 (0)	1 (0.04)	0 (0)	0 (0)	1 (0.04)
[redacted]	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)	1 (0.04)
Malaysia	0 (0)	1 (0.04)	1 (0.04)	0 (0)	3 (0.14)	5 (0.24)
Mexico	0 (0)	0 (0)	2 (0.09)	0 (0)	5 (0.24)	7 (0.33)
Oman	1 (0.04)	1 (0.04)	0 (0)	0 (0)	0 (0)	2 (0.09)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Saudi Arabia	0 (0)	1 (0.04)	3 (0.14)	0 (0)	1 (0.04)	5 (0.24)
Sri Lanka	0 (0)	0 (0)	6 (0.29)	0 (0)	0 (0)	6 (0.29)
[redacted]	0 (0)	0 (0)	1 (0.04)	0 (0)	0 (0)	1 (0.04)
Taiwan	4 (0.19)	0 (0)	0 (0)	0 (0)	3 (0.14)	7 (0.33)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
United States	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.29)	6 (0.29)
[redacted]	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)	1 (0.04)
[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Seriousness						
Serious	283 (13.73)	334 (16.22)	711 (34.51)	1 (0.04)	722 (35.04)	2051 (99.61)
Non-serious	0 (0)	0 (0)	3 (0.14)	0 (0)	5 (0.24)	8 (0.38)
Medical confirmation						
Medically confirmed	246 (11.94)	279 (13.55)	496 (24.07)	1 (0.04)	422 (20.48)	1444 (70.13)
Consumer reports	36 (1.74)	56 (2.71)	218 (10.58)	0 (0)	305 (14.80)	615 (29.85)

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Dose						
Dose 1	273	290	612	1	671	1847
Dose 2	9	45	102		55	211
Dose 3					1	1
Median Time to onset in days: AZD1222 Dose 1	11	13	12	9	12	12
Median Time to onset in days: AZD1222 Dose 2	14	12	13	NA	6	13
Thrombosis site						
Embolic and thrombotic events, arterial (SMQ)	51	49	104	1	104	309
Embolic and thrombotic events, venous (SMQ)	230	266	541	NA	423	1460
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)	132	138	270	1	339	88
Multiple site of thrombosis	118	103	180	1	146	548
Embolic and thrombotic events, venous (SMQ)						
Axillary vein thrombosis					1	1
Budd-Chiari syndrome	1		1			2
Cavernous sinus thrombosis	1	1	1		3	6
Cerebral venous sinus thrombosis	87	72	119		104	382

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Cerebral venous thrombosis	26	13	41		24	104
Deep vein thrombosis	41	59	157		102	359
Embolism venous	3	2			1	6
Hepatic vein embolism			1			1
Hepatic vein occlusion		1				1
Hepatic vein thrombosis	5	9	9		10	33
Jugular vein occlusion	2				1	3
Jugular vein thrombosis	10	5	14		14	43
Mesenteric vein thrombosis	10	10	14		11	45
Ophthalmic vein thrombosis		2	4		1	7
Ovarian vein thrombosis		1	2		1	4
Pelvic venous thrombosis	4	5	8		6	23
Peripheral vein occlusion					1	1
Portal vein cavernous transformation			1			1
Portal vein embolism					1	1
Portal vein occlusion	1		2			3
Portal vein thrombosis	32	28	47		44	151
Portosplenomesenteric venous thrombosis	1	1	3		6	11

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Post thrombotic syndrome	1					1
Pulmonary embolism	95	147	236		179	657
Pulmonary infarction	4	2	4		6	16
Pulmonary thrombosis	4		5		7	16
Pulmonary venous thrombosis			1		1	2
Renal vein embolism	1					1
Renal vein thrombosis	3	7	4		3	17
Retinal vein occlusion	1		2		3	6
Retinal vein thrombosis			1		2	3
Splenic vein occlusion			1			1
Splenic vein thrombosis	7	10	10		10	37
Subclavian vein thrombosis			1			1
Superficial vein thrombosis	6	5	9		8	28
Superior sagittal sinus thrombosis	17	4	24		9	54
Thrombophlebitis	1	3	5		8	17
Transverse sinus thrombosis	8	3	7		5	23
Vena cava filter insertion					1	1
Vena cava thrombosis		2	2		1	5
Venoocclusive liver disease			1			1

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Venous occlusion					1	1
Venous thrombosis	6	9	12		15	42
Venous thrombosis limb	1	1	1		7	10
Visceral venous thrombosis	11	5	8		5	29
Embolic and thrombotic events, arterial (SMQ)						
Acute myocardial infarction	4	6	10		5	25
Aortic embolus	1	3	3		2	9
Aortic thrombosis	11	5	14	1	6	37
Arterial occlusive disease			1		1	2
Arterial thrombosis	6	7	6		7	26
Carotid artery occlusion	2	1			3	6
Carotid artery thrombosis	7	6	9		6	28
Cerebral artery embolism			1		1	2
Cerebral artery occlusion	4	1	1			6
Cerebral artery thrombosis	3	3	8		3	17
Cerebrovascular insufficiency	1					1
Coronary artery bypass					1	1
Coronary artery occlusion					1	1
Coronary artery thrombosis	3	2	5		1	11
Embolism arterial	1	2	1		1	5
Femoral artery embolism		1				1

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Hepatic artery thrombosis		2			1	3
Iliac artery occlusion				1		1
Internal capsule infarction			1			1
Ischaemic cerebral infarction	3		3		1	7
Ischaemic stroke	4	6	13		20	43
Lacunar infarction	1		1		2	4
Mesenteric artery thrombosis		2	1		1	4
Myocardial infarction	4	4	10		7	25
Peripheral arterial occlusive disease		1	2			3
Peripheral artery occlusion	2		7		1	10
Peripheral artery thrombosis	11	4	15		8	38
Peripheral embolism	1	1	2		3	7
Pulmonary artery occlusion			2			2
Pulmonary artery thrombosis	3	1	1		3	8
Renal artery occlusion				1		1
Renal artery thrombosis			2		1	3
Renal embolism		1				1
Retinal artery occlusion					2	2
Splenic artery thrombosis		2	2		2	6
Stress cardiomyopathy	1					1

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Subclavian artery thrombosis	1					1
Thromboembolectomy		1				1
Thrombotic microangiopathy	1				3	4
Thrombotic thrombocytopenic purpura	2	5	11		21	39
Transient ischaemic attack	1	1	3		12	17
Truncus coeliacus thrombosis					1	1
Vertebral artery thrombosis	1					1
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)						
Adrenal thrombosis	1	1				2
Antiphospholipid syndrome		1	4			5
Atrial thrombosis	1	1	2		1	5
Autoimmune heparin-induced thrombocytopenia	1					1
Brain stem infarction			1			1
Brain stem stroke					1	1
Cardiac ventricular thrombosis	2	2	2		3	9
Cerebellar infarction	1		2			3
Cerebral congestion			1			1
Cerebral infarction	8	9	23		15	55
Cerebral ischaemia	1	1	2		1	5

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Cerebral thrombosis	7	9	17		15	48
Cerebrovascular accident	9	5	29		38	81
Disseminated intravascular coagulation	11	17	9		21	58
Embolic cerebral infarction	1		1			2
Embolic stroke		1			1	2
Embolism	6	15	28		14	63
Foetal vascular malperfusion	1					1
Haemorrhagic adrenal infarction	2	1	2		1	6
Haemorrhagic cerebral infarction	2	5	2		1	10
Haemorrhagic infarction		1	4		4	9
Haemorrhagic stroke	4	2	6		7	19
Haemorrhagic transformation stroke	6	1	4		4	15
Haemorrhoids thrombosed					1	1
Hemiparesis	24	18	25		12	79
Hemiplegia	5	4	8		15	32
Heparin-induced thrombocytopenia	10	5	10		14	39
Hepatic infarction	1	1	2		1	5
Hepatic vascular thrombosis			1		6	7
Infarction	2		4		3	9
Intestinal infarction		2	4		2	8
Intracardiac thrombus	2	2	4		1	9

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Mesenteric vascular occlusion					1	1
Monoparesis	1	1	2			4
Monoplegia			1		1	2
Pancreatic infarction					1	1
Paraparesis		1				1
Post procedural stroke					1	1
Prosthetic cardiac valve thrombosis	1					1
Quadriparesis		2			1	3
Quadriplegia	1	1				2
Renal infarct	4	2	3	1	4	14
Renal vascular thrombosis	2		2			4
Splenic infarction	2	5	7		6	20
Splenic thrombosis	3		2		1	6
Thalamic infarction			1			1
Thrombectomy			1		1	2
Thrombosis	51	52	111		184	398
Thrombosis in device				1		1
Thrombosis mesenteric vessel	5	2	1			8
Thrombosis with thrombocytopenia syndrome	13	9	25		45	92
Thrombotic stroke		1	1		3	5
Vascular graft thrombosis			1			1
Vascular operation			1			1
Vascular stent thrombosis			2		1	3
Platelet Level						
<150 x 109/L	282	336	714	1	13	1346

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Reported as < 150 x 109/L, however value not provided	9	12	58			79
<50 x 109/L	161	158	256	1	7	583
100-150 x 109/L	30	77	212		3	322
50-100 x 109/L	82	88	188		3	361
>150 x 109/L or 'normal'					47	47
Unk					667	667
Co-Reported Events						
Coagulopathy	22	26	25	NA	40	113
Co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)-Narrow* (≥10 events)	170	143	235	NA	253	801
Immune thrombocytopenia	63	31	65		95	254
Cerebral haemorrhage	43	32	61		58	194
Haemorrhage	18	18	23		7	66
Subarachnoid haemorrhage	17	16	20		7	60
Haemorrhage intracranial	14	14	22		9	59
Disseminated intravascular coagulation	11	17	9		21	58
Contusion	9	10	23		11	53
Petechiae	7	10	17		12	46
Thrombotic thrombocytopenic purpura	2	5	11		21	39
Haemoptysis	6	8	8		2	24

Table 138 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All reports
Cerebral haematoma	6	6	3		6	21
Haematoma	3	4	7		7	21
Haemorrhagic stroke	4	2	6		7	19
Adrenal haemorrhage	6	4	4		1	15
Haemorrhagic transformation stroke	6	1	4		4	15
Rectal haemorrhage	5	3	3		2	13
Epistaxis		2	7		3	12
Haematuria	5	1	3		1	10
Haemorrhagic cerebral infarction	2	5	2		1	10

Table 139 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2059)

Venous or arterial thrombosis					PF4 Antibodies				D dimer level			
Platelet level	**No**	**Unk**	**Yes**	**Grand Total**	**No**	**pending/Unk**	**yes**	**Grand Total**	**Unk**	**Yes (<4000 ng/mL)**	**Yes (>4000 ng/mL)**	**Grand Total**
<150	9	4	1332	1345	285	619	442	1346	557	162	627	1346
>150			47	47	10	33	4	47	19	16	12	47
Unk	11	3	653	667	96	508	63	668	656	2	9	667
Grand Total	**20**	**7**	**2032**	**2059**	**391**	**1160**	**509**	**2060**	**1232**	**180**	**648**	**2060**
Dose 1												
<150	9	3	1177	1189	231	540	418	1189	482	135	572	1189
>150			38	38	8	27	3	38	17	12	9	38
Unk	11	3	607	621	89	471	61	621	614	1	6	621
Grand Total	**20**	**6**	**1822**	**1848**	**328**	**1038**	**482**	**1848**	**1113**	**148**	**587**	**1848**
Dose 2												
<150		1	156	157	54	79	24	157	75	27	55	157
>150			9	9	2	6	1	9	2	4	3	9
Unk			45	45	7	36	2	45	41	1	3	45
Grand Total		**1**	**210**	**211**	**63**	**121**	**27**	**211**	**118**	**32**	**61**	**211**
Fatal reports												
<150			226	226	30	123	73	226	94	6	126	226
>150			3	3		3		3	1		2	3
Unk	1	1	118	120	21	88	11	120	119		1	120

Table 139 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2059)

Venous or arterial thrombosis					PF4 Antibodies				D dimer level			
Platelet level	No	Unk	Yes	Grand Total	No	pending/Unk	yes	Grand Total	Unk	Yes (<4000 ng/mL)	Yes (>4000 ng/mL)	Grand Total
Grand Total	1	1	347	349	51	214	84	349	214	6	129	349

PF-4 Platelet Factor 4, N Number, Unk Unknown.

Table 140 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All doses																
	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	15 (3)	13 (4)	0 (0)	17 (5)	8 (3)	1 (1)	24 (3)	23 (4)	0 (0)	0 (0)	0 (0)	0 (0)	30 (6)	20 (4)	0 (0)	151 (33)
Age - 30-39 Yrs	24 (8)	21 (8)	0 (0)	18 (5)	10 (2)	0 (0)	42 (6)	26 (5)	0 (0)	0 (0)	0 (0)	0 (0)	45 (11)	25 (5)	0 (0)	211 (50)
Age - 40-49 Yrs	46 (7)	32 (3)	1 (0)	41 (11)	25 (2)	0 (0)	36 (11)	38 (1)	0 (0)	0 (0)	0 (0)	0 (0)	68 (15)	41 (8)	1 (0)	329 (58)
Age - 50-59 Yrs	35 (7)	30 (5)	0 (0)	36 (10)	34 (3)	2 (0)	83 (12)	59 (8)	1 (1)	0 (0)	0 (0)	0 (0)	53 (11)	44 (10)	0 (0)	377 (67)
Age - 60-69 Yrs	15 (3)	23 (2)	0 (0)	31 (5)	37 (9)	0 (0)	98 (21)	70 (5)	0 (0)	0 (0)	1 (1)	0 (0)	77 (9)	83 (10)	1 (1)	436 (66)
Age - 70-79 Yrs	9 (1)	4 (3)	0 (0)	19 (1)	21 (3)	0 (0)	47 (10)	76 (5)	0 (0)	0 (0)	0 (0)	0 (0)	41 (4)	53 (3)	1 (0)	271 (30)

Table 140 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All doses																
	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 80+ Yrs	3 (1)	1 (0)	0 (0)	7 (3)	8 (2)	0 (0)	24 (1)	28 (1)	0 (0)	0 (0)	0 (0)	0 (0)	20 (2)	21 (5)	0 (0)	112 (15)
Age Unknown	10 (1)	0 (0)	0 (0)	11 (3)	8 (1)	1 (0)	13 (3)	24 (2)	2 (0)	0 (0)	0 (0)	0 (0)	34 (8)	22 (3)	47 (8)	172 (29)
Grand Total	157 (31)	124 (25)	1 (0)	181 (44)	151 (25)	4 (1)	367 (67)	344 (31)	3 (1)	0 (0)	1 (1)	0 (0)	368 (66)	309 (48)	50 (9)	2060 (349)
Dose 1																
Age - 18-29 Yrs	15 (3)	13 (4)	0 (0)	17 (6)	8 (3)	1 (1)	23 (3)	22 (4)	0 (0)	0 (0)	0 (0)	0 (0)	30 (6)	19 (4)	0 (0)	148 (34)
Age - 30-39 Yrs	23 (8)	21 (8)	0 (0)	18 (5)	10 (2)	0 (0)	41 (6)	25 (5)	0 (0)	0 (0)	0 (0)	0 (0)	43 (11)	25 (5)	0 (0)	206 (50)
Age - 40-49 Yrs	46 (7)	32 (3)	1 (0)	39 (11)	23 (2)	0 (0)	34 (11)	32 (1)	0 (0)	0 (0)	0 (0)	0 (0)	65 (14)	38 (8)	1 (0)	311 (57)
Age - 50-59 Yrs	35 (7)	28 (5)	0 (0)	34 (10)	31 (3)	2 (0)	81 (12)	50 (6)	1 (1)	0 (0)	0 (0)	0 (0)	49 (11)	41 (10)	0 (0)	352 (65)
Age - 60-69 Yrs	15 (3)	21 (2)	0 (0)	30 (5)	28 (9)	0 (0)	85 (21)	58 (5)	0 (0)	0 (0)	1 (1)	0 (0)	72 (8)	68 (8)	1 (1)	379 (63)
Age - 70-79 Yrs	8 (1)	2 (1)	0 (0)	15 (1)	11 (0)	0 (0)	40 (8)	54 (4)	0 (0)	0 (0)	0 (0)	0 (0)	36 (4)	47 (2)	1 (0)	214 (21)
Age - 80+ Yrs	2 (1)	1 (0)	0 (0)	4 (2)	5 (1)	0 (0)	16 (1)	20 (1)	0 (0)	0 (0)	0 (0)	0 (0)	15 (2)	20 (5)	0 (0)	83 (13)

Table 140 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All doses																
	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age Unknown	10 (1)	0 (0)	0 (0)	7 (2)	7 (1)	1 (0)	13 (3)	16 (2)	1 (0)	0 (0)	0 (0)	0 (0)	34 (8)	19 (3)	47 (8)	155 (28)
Grand Total	154 (31)	118 (23)	1 (0)	164 (42)	123 (21)	4 (1)	333 (65)	277 (28)	2 (1)	0 (0)	1 (1)	0 (0)	344 (64)	277 (45)	50 (9)	1848 (331)
Dose 2																
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	4 (0)
Age - 30-39 Yrs	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	5 (0)
Age - 40-49 Yrs	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	2 (0)	6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	3 (0)	0 (0)	18 (1)
Age - 50-59 Yrs	0 (0)	2 (0)	0 (0)	2 (0)	3 (0)	0 (0)	2 (0)	9 (2)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0)	3 (0)	0 (0)	25 (2)
Age - 60-69 Yrs	0 (0)	2 (0)	0 (0)	1 (0)	9 (0)	0 (0)	13 (0)	12 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	15 (2)	0 (0)	57 (3)
Age - 70-79 Yrs	1 (0)	2 (2)	0 (0)	4 (0)	10 (3)	0 (0)	7 (2)	22 (1)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0)	6 (1)	0 (0)	56 (9)
Age - 80+ Yrs	1 (0)	0 (0)	0 (0)	3 (1)	3 (1)	0 (0)	8 (0)	8 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0)	1 (0)	0 (0)	29 (2)

Table 140 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All doses																
	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age category /Gender	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	**F**	**M**	**U**	
Age Unknown	0 (0)	0 (0)	0 (0)	4 (1)	1 (0)	0 (0)	0 (0)	8 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	0 (0)	17 (1)
Grand Total	**0 (0)**	**6 (2)**	**0 (0)**	**17 (2)**	**28 (4)**	**0 (0)**	**34 (2)**	**67 (3)**	**1 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**23 (2)**	**32 (3)**	**0 (0)**	**211 (18)**

F Female, M Male , yrs Years

Fatal cases

Seventeen percent (348 out of 2059) of TTS cases reported fatal outcome. Age and gender stratification for fatal reports is presented in Table 141.

Table 141 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, and fatality

Age group	Female N (fatal cases)	Male N (fatal cases)	Unknown Gender N (Fatal cases)	Grand Total
Age - 18-29 Yrs	86 (17)	64 (15)	1 (1)	151 (33)
Age - 30-39 Yrs	129 (30)	82 (20)	0 (0)	211 (50)
Age - 40-49 Yrs	191 (44)	136 (14)	2 (0)	329 (58)
Age - 50-59 Yrs	207 (40)	167 (26)	3 (1)	377 (67)
Age - 60-69 Yrs	221 (38)	214 (27)	1 (1)	436 (66)
Age - 70-79 Yrs	116 (16)	154 (14)	1 (0)	271 (30)
Age - 80+ Yrs	54 (7)	58 (8)	0 (0)	112 (15)
Age Unknown	68 (15)	54 (6)	50 (8)	172 (29)
Grand Total	1072 (207)	929 (130)	58 (11)	2059 (348)

N Number, yrs Years.

TTO was available in 268 of the 348 fatal reports and ranged from 0 – 121 days with a median TTO of 11 days. Of the 348 fatal events, 330 fatal reports occurred after Dose 1 and 18 fatal case reports occurred after Dose 2. TTO was available in 17 reports after Dose 2 with a range of 0 – 56 days and a median of 14 days.

The most frequently reported events of thrombosis in the fatal reports were: Cerebral venous sinus thrombosis (100), followed by (>10) Thrombosis (68), Pulmonary embolism (65), Cerebral venous thrombosis (36), Portal vein thrombosis (32), Hemiparesis (31), Cerebrovascular accident (24), Cerebral thrombosis (21), Thrombosis with thrombocytopenia syndrome (21), Cerebral infarction (17), Deep vein thrombosis (15),Superior sagittal sinus thrombosis (14), Haemorrhagic stroke (12), Mesenteric vein thrombosis (11), and Ischaemic stroke (11), Hemiplegia (11) and Transverse sinus thrombosis (11). The highest number of the fatal cases were due to HLT: Cerebrovascular and venous sinus thrombosis (150/349, 43%) and the Cerebral haemorrhage was the most common bleeding event associated with fatal event.

A total of 135 of the 348 fatal case reports reported multiple sites of thrombosis. In 211 of the 348 fatal case reports, there was only one site of thrombosis. In 17 case reports, there was a

reported PT from all 3 arterial, venous and vessel type unspecified and mixed arterial and venous SMQ. More than one vessel type was involved in 118 case reports.

In 224 out of 348 fatal reports (64%), there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). Most common (>10) bleeding events included Cerebral haemorrhage (101), Immune thrombocytopenia (50), Subarachnoid haemorrhage (27), Haemorrhage intracranial (27), Haemorrhagic stroke (12), Haemorrhage (11), Cerebral hematoma (11), and Contusion (11). Thirty-five (35) case reports had the co-reported events from the HLT: Coagulopathies, including 23 cases with DIC.

Fatality/survival rate over time

Fatality/survival rate over time was calculated based on the case onset date. The onset date was not reported in 386 of the 2060 case reports, and for 81 case reports with fatal outcome. In cases where the onset date was not reported, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. Fatality/survival rate cumulatively for each month up to 28 December 2021 is presented in Table 142 and Figure 2.

The total number and percent of fatal reports since April 2021 are decreasing compared to January 2021-March 2021. There is an increased fatality rate in December 2021 (4 reported fatal events out of 14 reports) compared to the earlier months. However, vaccination in these 4 fatal cases occurred prior to December 2021, but were reported in December 2021 with unknown event onset dates, which could explain the reason for the increased fatality rate. Two of the 4 reports (PPD) originated from PPD with the date of vaccination reported as PPD and PPD , respectively. Event onset date and/or time to onset was not reported in either of these cases. The 3rd case (PPD) originated from PPD and contained limited information with no reported vaccination dates, event onset dates, or time to event onset reported. The 4th case (PPD) originated from PPD and contained limited information with no reported vaccination dates, event dates, or information regarding time to event onset. This 4th case is a potential duplicate report of a previously reported case.

Number and percent of fatal reports since April 2021 has decreased compared to January-March 2021, which suggests the effectiveness of the diagnostic and treatment guidelines implemented (ASH 2021, EHP 2021 and Thaler et al 2021) in March 2021.

Table 142 TTS fatality/survival rate over time

Case onset month [a]	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
January 2021	14	8	22	36.4
February 2021	72	25	97	25.8

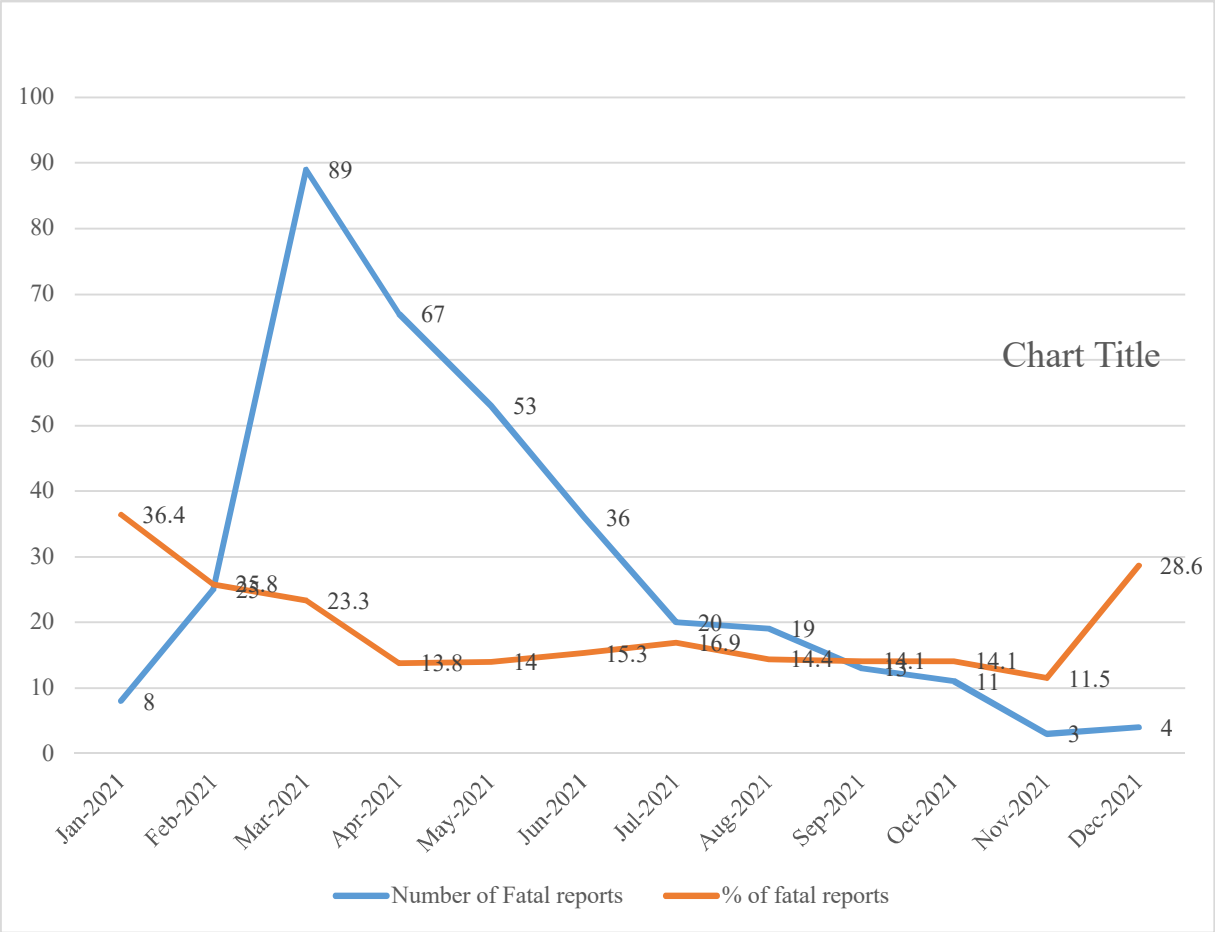
Table 142 TTS fatality/survival rate over time

Case onset month [a]	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
March 2021	293	89	382	23.3
April 2021	418	67	485	13.8
May 2021	325	53	378	14
June 2021	199	36	235	15.3
July 2021	98	20	118	16.9
August 2021	113	19	132	14.4
September 2021	79	13	92	14.1
October 2021	67	11	78	14.1
November 2021	23	3	26	11.5
December 2021	10	4	14	28.6
Grand Total	1711	348	2059	16.9

[a] In cases where case onset date was not available, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time.

TTS Thrombosis with thrombocytopenia syndrome.

Figure 2 TTS fatality/survival rate over time



Fatality rate over time by age group/gender for all cases is presented in Table 143 and fatality rate over time by age group/gender and doses (separately for all doses, dose 1 and dose 2) for confirmed/probable/possible cases is presented in Table 144.

Fatality rate in female vaccinees is higher (60%) compared to male (37%) for all cases and fatality rate in confirmed/probable/possible cases, is higher in female compared to male for all doses (63% vs 36%) and dose 1 (65% vs 34%) but for dose 2, fatality rate in female is less than male (31% vs 69%), the reason for this difference might be cases received with dose 2 are very little and this would increase the percentage markedly.

For all cases, highest fatality rate in female vaccinees was 21% in 40-49 years and 19% in 50-59 years age group, while in male vaccinees the highest fatality rate was 20% in 50-59 years and 21% in 60-69 years age group. In confirmed/probable/possible cases, highest fatality rate in female vaccinees was 20% in 40-49 years, 50-59 years and 60 to 69 years age groups (all doses) and 21% in 40-49 years, 50-59 years and 60 to 69 years age groups (dose 1) and 50%

in 70-79 years age group (dose 2), while in male vaccinees highest fatality rate in male vaccinees was 20% in 50-59 years and 60-69 years (all doses) and 22% in 60 to 69 years age group (dose 1) and 67% in 70-79 years age group (dose 2). Fatality rate for some age groups/gender/months is increased compared to the previous period, however reports received for these age groups/gender/months did not have onset dates of events and case received date was considered for analysis. This may be the reason for increased fatality rate, also cases received for these months are very little and this would increase the percentages markedly.

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
Age - 18-29 Yrs													
February-2021	3	1	25	2	1	33.3	0	0	0	5	2	7	28.6
March 2021	23	2	8	6	4	40	0	0	0	29	6	35	17.1
April 2021	14	0	0	17	3	15	0	0	0	31	3	34	8.8
May 2021	2	0	0	6	1	14.3	0	0	0	8	1	9	11.1
June 2021	3	5	62.5	8	2	20	0	1	100	11	8	19	42.1
July 2021	4	2	33.3	3	0	0	0	0	0	7	2	9	22.2
August 2021	10	4	28.6	3	1	25	0	0	0	13	5	18	27.8
September 2021	1	1	50	2	1	33.3	0	0	0	3	2	5	40
October 2021	6	0	0	2	1	33.3	0	0	0	8	1	9	11.1
November 2021	3	0	0	0	1	100	0	0	0	3	1	4	25
December 2021	0	2	100	0	0	0	0	0	0	0	2	2	100
Age - 30-39 Yrs													
January 2021	2	1	33.3	1	2	66.7	0	0	0	3	3	6	50

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
February 2021	4	2	33.3	4	1	20	0	0	0	8	3	11	27.3
March 2021	31	8	20.5	10	5	33.3	0	0	0	41	13	54	24.1
April 2021	22	3	12	9	5	35.7	0	0	0	31	8	39	20.5
May 2021	14	5	26.3	9	0	0	0	0	0	23	5	28	17.9
June 2021	9	4	30.8	10	3	23.1	0	0	0	19	7	26	26.9
July 2021	5	3	37.5	4	1	20	0	0	0	9	4	13	30.8
August 2021	7	1	12.5	5	1	16.7	0	0	0	12	2	14	14.3
September 2021	2	1	33.3	5	2	28.6	0	0	0	7	3	10	30
October 2021	1	2	66.7	2	0	0	0	0	0	3	2	5	40
November 2021	2	0	0	2	0	0	0	0	0	4	0	4	0
December 2021	0	0	0	1	0	0	0	0	0	1	0	1	0
Age - 40-49 Yrs													
February 2021	5	4	44.4	2	0	0	0	0	0	7	4	11	36.4
March 2021	29	17	37	18	2	10	0	0	0	47	19	66	28.8

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
April 2021	39	6	13.3	24	3	11.1	1	0	0	64	9	73	12.3
May 2021	37	6	14	44	4	8.3	1	0	0	82	10	92	10.9
June 2021	15	5	25	14	1	6.7	0	0	0	29	6	35	17.1
July 2021	3	2	40	2	2	50	0	0	0	5	4	9	44.4
August 2021	2	2	50	3	1	25	0	0	0	5	3	8	37.5
September 2021	5	1	16.7	9	0	0	0	0	0	14	1	15	6.7
October 2021	8	0	0	5	1	16.7	0	0	0	13	1	14	7.1
November 2021	4	1	20	1	0	0	0	0	0	5	1	6	16.7
Age - 50-59 Yrs													
January 2021	3	2	40	0	0	0	0	0	0	3	2	5	40
February 2021	8	1	11.1	5	0	0	0	0	0	13	1	14	7.1
March 2021	46	16	25.8	25	8	24.2	0	0	0	71	24	95	25.3
April 2021	43	5	10.4	41	6	12.8	2	0	0	86	11	97	11.3
May 2021	25	1	3.8	21	5	19.2	0	0	0	46	6	52	11.5
June 2021	15	5	25	22	3	12	0	1	100	37	9	46	19.6

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
July 2021	8	1	11.1	8	1	11.1	0	0	0	16	2	18	11.1
August 2021	7	4	36.4	9	1	10	0	0	0	16	5	21	23.8
September 2021	4	3	42.9	8	0	0	0	0	0	12	3	15	20
October 2021	5	1	16.7	2	2	50	0	0	0	7	3	10	30
November 2021	2	1	33.3	0	0	0	0	0	0	2	1	3	33.3
December 2021	1	0	0	0	0	0	0	0	0	1	0	1	0
Age - 60-69 Yrs													
January 2021	0	0	0	3	2	40	0	0	0	3	2	5	40
February 2021	7	8	53.3	5	1	16.7	0	0	0	12	9	21	42.9
March 2021	35	8	18.6	29	5	14.7	0	0	0	64	13	77	16.9
April 2021	48	9	15.8	38	7	15.6	0	0	0	86	16	102	15.7
May 2021	42	11	20.8	39	9	18.8	0	1	100	81	21	102	20.6
June 2021	25	1	3.8	19	0	0	0	0	0	44	1	45	2.2
July 2021	6	0	0	12	1	7.7	0	0	0	18	1	19	5.3

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
August 2021	12	0	0	16	1	5.9	0	0	0	28	1	29	3.4
September 2021	3	1	25	11	0	0	0	0	0	14	1	15	6.7
October 2021	2	0	0	12	1	7.7	0	0	0	14	1	15	6.7
November 2021	1	0	0	1	0	0	0	0	0	2	0	2	0
December 2021	2	0	0	2	0	0	0	0	0	4	0	4	0
Age - 70-79 Yrs													
January 2021	2	0	0	3	0	0	0	0	0	5	0	5	0
February 2021	14	1	6.7	6	2	25	0	0	0	20	3	23	13
March 2021	9	3	25	5	1	16.7	0	0	0	14	4	18	22.2
April 2021	31	7	18.4	38	3	7.3	1	0	0	70	10	80	12.5
May 2021	13	2	13.3	28	4	12.5	0	0	0	41	6	47	12.8
June 2021	12	1	7.7	14	1	6.7	0	0	0	26	2	28	7.1
July 2021	7	1	12.5	14	2	12.5	0	0	0	21	3	24	12.5
August 2021	6	1	14.3	11	0	0	0	0	0	17	1	18	5.6

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
September 2021	3	0	0	11	1	8.3	0	0	0	14	1	15	6.7
October 2021	2	0	0	7	0	0	0	0	0	9	0	9	0
November 2021	1	0	0	2	0	0	0	0	0	3	0	3	0
December 2021	0	0	0	1	0	0	0	0	0	1	0	1	0
Age - 80+ Yrs													
January 2021	0	0	0	0	1	100	0	0	0	0	1	1	100
February 2021	2	1	33.3	0	2	100	0	0	0	2	3	5	60
March 2021	2	1	33.3	4	4	50	0	0	0	6	5	11	45.5
April 2021	12	4	25	13	1	7.1	0	0	0	25	5	30	16.7
May 2021	5	0	0	6	0	0	0	0	0	11	0	11	0
June 2021	7	1	12.5	6	0	0	0	0	0	13	1	14	7.1
July 2021	10	0	0	2	0	0	0	0	0	12	0	12	0
August 2021	4	0	0	10	0	0	0	0	0	14	0	14	0
September 2021	5	0	0	3	0	0	0	0	0	8	0	8	0

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
October 2021	0	0	0	3	0	0	0	0	0	3	0	3	0
November 2021	0	0	0	2	0	0	0	0	0	2	0	2	0
December 2021	0	0	0	1	0	0	0	0	0	1	0	1	0
Age Unknown													
February 2021	4	0	0	1	0	0	0	0	0	5	0	5	0
March 2021	11	2	15.4	4	3	42.9	6	0	0	21	5	26	19.2
April 2021	11	4	26.7	10	1	9.1	4	0	0	25	5	30	16.7
May 2021	11	1	8.3	8	1	11.1	14	2	12.5	33	4	37	10.8
June 2021	4	2	33.3	9	0	0	7	0	0	20	2	22	9.1
July 2021	3	3	50	7	1	12.5	0	0	0	10	4	14	28.6
August 2021	3	0	0	5	0	0	0	2	100	8	2	10	20
September 2021	2	1	33.3	2	0	0	3	1	25	7	2	9	22.2
October 2021	2	1	33.3	1	0	0	7	2	22.2	10	3	13	23.1
November 2021	1	0	0	1	0	0	0	0	0	2	0	2	0

Table 143 TTS fatality/survival rate over time by age group/gender for all cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
December 2021	1	1	50	0	0	0	1	1	50	2	2	4	50
Grand Total	865	207	19.4	799	130	14	47	11	19	1711	348	2059	16.9

TTS Thrombosis with thrombocytopenia syndrome.

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
Age - 18-29 Yrs													
February 2021	2	1	33.3	1	1	50			NA	3	2	5	40
March 2021	15	2	11.8	5	3	37.5			NA	20	5	25	20
April 2021	11		0	14	2	12.5			NA	25	2	27	7.4
May 2021	2		0	3	1	25			NA	5	1	6	16.7
June 2021	3	3	50	3	2	40		1	100	6	6	12	50

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
July 2021	4	1	20	2		0			NA	6	1	7	14.3
August 2021	5	3	37.5	2	1	33.3			NA	7	4	11	36.4
September 2021	1	1	50	2	1	33.3			NA	3	2	5	40
October 2021	1		0	1		0			NA	2		2	0
November 2021	1		0			NA			NA	1		1	0
December 2021			NA			NA			NA				NA
Age - 30-39 Yrs													
January 2021	1	1	50	1	2	66.7			NA	2	3	5	60
February 2021	4	2	33.3	1	1	50			NA	5	3	8	37.5
March 2021	20	6	23.1	7	4	36.4			NA	27	10	37	27
April 2021	16	2	11.1	7	4	36.4			NA	23	6	29	20.7
May 2021	11	4	26.7	7		0			NA	18	4	22	18.2
June 2021	1		0	3	1	25			NA	4	1	5	20
July 2021	5	1	16.7	4	1	20			NA	9	2	11	18.2
August 2021	3	1	25	4	1	20			NA	7	2	9	22.2
September 2021	1	1	50	3	1	25			NA	4	2	6	33.3

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
October 2021	1	1	50	2		0			NA	3	1	4	25
November 2021	2		0	2		0			NA	4		4	0
December 2021			NA	1		0			NA	1		1	0
Age - 40-49 Yrs													
February 2021	3	3	50	2		0			NA	5	3	8	37.5
March 2021	18	14	43.8	12		0			NA	30	14	44	31.8
April 2021	26	2	7.1	18	1	5.3			NA	44	3	47	6.4
May 2021	25	5	16.7	35	3	7.9	1		0	61	8	69	11.6
June 2021	5	2	28.6	7		0			NA	12	2	14	14.3
July 2021	3	1	25	1	1	50			NA	4	2	6	33.3
August 2021	1		0	1		0			NA	2		2	0
September 2021	4	1	20	8		0			NA	12	1	13	7.7
October 2021	5		0	4	1	20			NA	9	1	10	10
November 2021	4	1	20	1		0			NA	5	1	6	16.7
Age - 50-59 Yrs													

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
January 2021	2	1	33.3			NA			NA	2	1	3	33.3
February 2021	6	1	14.3	4		0			NA	10	1	11	9.1
March 2021	35	13	27.1	20	3	13			NA	55	16	71	22.5
April 2021	33	3	8.3	35	5	12.5	2		0	70	8	78	10.3
May 2021	17		0	17	2	10.5			NA	34	2	36	5.6
June 2021	12	4	25	14	2	12.5		1	100	26	7	33	21.2
July 2021	6	1	14.3	5	1	16.7			NA	11	2	13	15.4
August 2021	3	4	57.1	6	1	14.3			NA	9	5	14	35.7
September 2021	4	1	20	5		0			NA	9	1	10	10
October 2021	4		0	1	2	66.7			NA	5	2	7	28.6
November 2021	2	1	33.3			NA			NA	2	1	3	33.3
December 2021	1		0			NA			NA	1		1	0
Age - 60-69 Yrs													
January 2021			NA	2	2	50			NA	2	2	4	50
February 2021	5	7	58.3	4	1	20			NA	9	8	17	47.1

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
March 2021	26	7	21.2	20	2	9.1			NA	46	9	55	16.4
April 2021	24	5	17.2	23	5	17.9			NA	47	10	57	17.5
May 2021	27	9	25	25	5	16.7			NA	52	14	66	21.2
June 2021	16		0	10		0			NA	26		26	0
July 2021	4		0	5		0			NA	9		9	0
August 2021	10		0	6		0			NA	16		16	0
September 2021	2	1	33.3	9		0			NA	11	1	12	8.3
October 2021	1		0	10	1	9.1			NA	11	1	12	8.3
Age - 70-79 Yrs													
January 2021	2		0	2		0			NA	4		4	0
February 2021	11	1	8.3	6	2	25			NA	17	3	20	15
March 2021	5	1	16.7	4	1	20			NA	9	2	11	18.2
April 2021	14	6	30	24	2	7.7			NA	38	8	46	17.4
May 2021	8	1	11.1	16	3	15.8			NA	24	4	28	14.3
June 2021	9	1	10	6	1	14.3			NA	15	2	17	11.8
July 2021	7	1	12.5	9	1	10			NA	16	2	18	11.1
August 2021	3	1	25	8		0			NA	11	1	12	8.3
September 2021	2		0	6	1	14.3			NA	8	1	9	11.1

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
October 2021	2		0	7		0			NA	9		9	0
November 2021			NA	2		0			NA	2		2	0
Age - 80+ Yrs													
February 2021	1	1	50		1	100			NA	1	2	3	66.7
March 2021	1	1	50	2	1	33.3			NA	3	2	5	40
April 2021	8	3	27.3	8	1	11.1			NA	16	4	20	20
May 2021	4		0	2		0			NA	6		6	0
June 2021	1		0	5		0			NA	6		6	0
July 2021	6		0	2		0			NA	8		8	0
August 2021	3		0	7		0			NA	10		10	0
September 2021	5		0	3		0			NA	8		8	0
October 2021			NA	3		0			NA	3		3	0
November 2021			NA	2		0			NA	2		2	0
Age Unknown													
February 2021	2		0			NA			NA	2		2	0

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
March 2021	6	1	14.3	3	1	25	1		0	10	2	12	16.7
April 2021	7	2	22.2	6	1	14.3			NA	13	3	16	18.8
May 2021	5	1	16.7	6	1	14.3	1		0	12	2	14	14.3
June 2021	3	1	25	7		0	1		0	11	1	12	8.3
July 2021		2	100	1		0			NA	1	2	3	66.7
August 2021	2		0	4		0			NA	6		6	0
September 2021			NA	1		0			NA	1		1	0
October 2021	1		0			NA			NA	1		1	0
November 2021	1		0	1		0			NA	2		2	0
Grand Total	563	141	20.1	538	81	13.1	6	2	25	1107	224	1331	16.9
Dose 1													
Age - 18-29 Yrs													
February 2021	2	1	33.3	1	1	50			NA	3	2	5	40
March 2021	15	2	11.8	5	3	37.5			NA	20	5	25	20
April 2021	11		0	14	2	12.5			NA	25	2	27	7.4
May 2021	2		0	2	1	33.3			NA	4	1	5	20
June 2021	3	3	50	3	2	40		1	100	6	6	12	50
July 2021	3	1	25	2		0			NA	5	1	6	16.7

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
August 2021	4	3	42.9	2	1	33.3			NA	6	4	10	40
September 2021	1	1	50	2	1	33.3			NA	3	2	5	40
October 2021	1		0	1		0			NA	2		2	0
November 2021	1		0			NA			NA	1		1	0
December 2021		0	NA			NA			NA		0	0	NA
Age - 30-39 Yrs													
January 2021	1	1	50	1	2	66.7			NA	2	3	5	60
February 2021	4	2	33.3	1	1	50			NA	5	3	8	37.5
March 2021	20	6	23.1	7	4	36.4			NA	27	10	37	27
April 2021	16	2	11.1	7	4	36.4			NA	23	6	29	20.7
May 2021	10	4	28.6	6		0			NA	16	4	20	20
June 2021	1		0	3	1	25			NA	4	1	5	20
July 2021	5	1	16.7	4	1	20			NA	9	2	11	18.2
August 2021	3	1	25	4	1	20			NA	7	2	9	22.2
September 2021	1	1	50	3	1	25			NA	4	2	6	33.3

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
October 2021		1	100	2		0			NA	2	1	3	33.3
November 2021	2		0	2		0			NA	4		4	0
December 2021			NA	1		0			NA	1		1	0
Age - 40-49 Yrs													
February 2021	3	3	50	2		0			NA	5	3	8	37.5
March 2021	18	14	43.8	12		0			NA	30	14	44	31.8
April 2021	25	2	7.4	18	1	5.3			NA	43	3	46	6.5
May 2021	23	5	17.9	32	3	8.6	1		0	56	8	64	12.5
June 2021	5	2	28.6	5		0			NA	10	2	12	16.7
July 2021	3	1	25		1	100			NA	3	2	5	40
August 2021	1		0	1		0			NA	2		2	0
September 2021	4	1	20	8		0			NA	12	1	13	7.7
October 2021	5		0	2	1	33.3			NA	7	1	8	12.5
November 2021	3	1	25	1		0			NA	4	1	5	20
Age - 50-59 Yrs													

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
January 2021	2	1	33.3			NA			NA	2	1	3	33.3
February 2021	6	1	14.3	4		0			NA	10	1	11	9.1
March 2021	34	13	27.7	19	3	13.6			NA	53	16	69	23.2
April 2021	33	3	8.3	35	5	12.5	2		0	70	8	78	10.3
May 2021	17		0	16	1	5.9			NA	33	1	34	2.9
June 2021	11	4	26.7	12	1	7.7		1	100	23	6	29	20.7
July 2021	5	1	16.7	2	1	33.3			NA	7	2	9	22.2
August 2021	3	4	57.1	3	1	25			NA	6	5	11	45.5
September 2021	4	1	20	3		0			NA	7	1	8	12.5
October 2021	3		0	1	2	66.7			NA	4	2	6	33.3
November 2021	2	1	33.3			NA			NA	2	1	3	33.3
December 2021	1		0			NA			NA	1		1	0
Age - 60-69 Yrs													
January 2021			NA	1	2	66.7			NA	1	2	3	66.7
February 2021	5	7	58.3	4	1	20			NA	9	8	17	47.1

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
March 2021	26	7	21.2	20	2	9.1			NA	46	9	55	16.4
April 2021	23	5	17.9	21	5	19.2			NA	44	10	54	18.5
May 2021	22	9	29	18	5	21.7			NA	40	14	54	25.9
June 2021	13		0	9		0			NA	22		22	0
July 2021	4		0	3		0			NA	7		7	0
August 2021	6		0	3		0			NA	9		9	0
September 2021	1	1	50	5		0			NA	6	1	7	14.3
October 2021	1		0	7	1	12.5			NA	8	1	9	11.1
Age - 70-79 Yrs													
January 2021	2		0	2		0			NA	4		4	0
February 2021	11	1	8.3	5	2	28.6			NA	16	3	19	15.8
March 2021	4	1	20	4	1	20			NA	8	2	10	20
April 2021	11	5	31.3	18	1	5.3			NA	29	6	35	17.1
May 2021	6	1	14.3	9		0			NA	15	1	16	6.3
June 2021	8	1	11.1	4		0			NA	12	1	13	7.7
July 2021	5	1	16.7	6	1	14.3			NA	11	2	13	15.4
August 2021	3		0	7		0			NA	10		10	0
September 2021	2		0	2		0			NA	4		4	0

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
October 2021	1		0	5		0			NA	6		6	0
Age - 80+ Yrs													
February 2021	1	1	50		1	100			NA	1	2	3	66.7
March 2021	1		0	1	1	50			NA	2	1	3	33.3
April 2021	5	3	37.5	5		0			NA	10	3	13	23.1
May 2021	3		0	2		0			NA	5		5	0
June 2021			NA	5		0			NA	5		5	0
July 2021	3		0	2		0			NA	5		5	0
August 2021	2		0	4		0			NA	6		6	0
September 2021	3		0	1		0			NA	4		4	0
October 2021			NA	2		0			NA	2		2	0
November 2021			NA	2		0			NA	2		2	0
Age Unknown													
February 2021	2		0			NA			NA	2		2	0
March 2021	6	1	14.3	3	1	25	1		0	10	2	12	16.7
April 2021	6	2	25	6	1	14.3			NA	12	3	15	20

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
May 2021	3	1	25	4	1	20			NA	7	2	9	22.2
June 2021	3	1	25	2		0	1		0	6	1	7	14.3
July 2021		1	100	1		0			NA	1	1	2	50
August 2021	2		0	3		0			NA	5		5	0
October 2021	1		0			NA			NA	1		1	0
November 2021	1		0	1		0			NA	2		2	0
Grand Total	513	137	21.2	446	72	13.9	5	2	28.6	964	211	1175	18
Dose 2													
Age - 18-29 Yrs													
May 2021			NA	1		0			NA	1		1	0
July 2021	1		0			NA			NA	1		1	0
August 2021	1		0			NA			NA	1		1	0
Age - 30-39 Yrs													
May 2021	1		0	1		0			NA	2		2	0
October 2021	1		0			NA			NA	1		1	0
Age - 40-49 Yrs													
April 2021	1		0			NA			NA	1		1	0
May 2021	2		0	3		0			NA	5		5	0

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
June 2021			NA	2		0			NA	2		2	0
July 2021			NA	1		0			NA	1		1	0
October 2021			NA	2		0			NA	2		2	0
November 2021	1		0			NA			NA	1		1	0
Age - 50-59 Yrs													
March 2021	1		0	1		0			NA	2		2	0
May 2021			NA	1	1	50			NA	1	1	2	50
June 2021	1		0	2	1	33.3			NA	3	1	4	25
July 2021	1		0	3		0			NA	4		4	0
August 2021			NA	3		0			NA	3		3	0
September 2021			NA	2		0			NA	2		2	0
October 2021	1		0			NA			NA	1		1	0
Age - 60-69 Yrs													
January 2021			NA	1		0			NA	1		1	0
April 2021	1		0	2		0			NA	3		3	0
May 2021	5		0	7		0			NA	12		12	0
June 2021	3		0	1		0			NA	4		4	0

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
July 2021			NA	2		0			NA	2		2	0
August 2021	4		0	3		0			NA	7		7	0
September 2021	1		0	4		0			NA	5		5	0
October 2021			NA	3		0			NA	3		3	0
Age - 70-79 Yrs													
February 2021			NA	1		0			NA	1		1	0
March 2021	1		0			NA			NA	1		1	0
April 2021	3	1	25	6	1	14.3			NA	9	2	11	18.2
May 2021	2		0	7	3	30			NA	9	3	12	25
June 2021	1		0	2	1	33.3			NA	3	1	4	25
July 2021	2		0	3		0			NA	5		5	0
August 2021		1	100	1		0			NA	1	1	2	50
September 2021			NA	4	1	20			NA	4	1	5	20
October 2021	1		0	2		0			NA	3		3	0
November 2021			NA	2		0			NA	2		2	0
Age - 80+ Yrs													

Table 144 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	Female			Male			Unknown			Grand total			
March 2021		1	100	1		0			NA	1	1	2	50
April 2021	3		0	3	1	25			NA	6	1	7	14.3
May 2021	1		0			NA			NA	1		1	0
June 2021	1		0			NA			NA	1		1	0
July 2021	3		0			NA			NA	3		3	0
August 2021	1		0	3		0			NA	4		4	0
September 2021	2		0	2		0			NA	4		4	0
October 2021			NA	1		0			NA	1		1	0
Age Unknown													
April 2021	1		0			NA			NA	1		1	0
May 2021	2		0	2		0	1		0	5		5	0
June 2021			NA	5		0			NA	5		5	0
July 2021		1	100			NA			NA		1	1	100
August 2021			NA	1		0			NA	1		1	0
September 2021			NA	1		0			NA	1		1	0
Grand Total	50	4	7.4	92	9	4.5	1		0	143	13	156	8.3

NA Not Applicable, yrs Years

TTS reports after Dose 2 of COVID-19 VACCINE ASTRAZENECA

A search of the AstraZeneca global safety database was undertaken to retrieve adverse event reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 2 of the COVID-19 VACCINE ASTRAZENECA. The search encompassed all cases retrieved up to 28 December 2021. The search criteria mentioned above was used to identify TTS cases post dose 2. The cases of TTS following the dose 2 were confirmed based on the dose number/information provided in the narrative, if the reports did not contain information on dose 2, they were not included in the below analysis. The search identified 211 cumulative cases of TTS following the second dose of COVID-19 VACCINE ASTRAZENECA. Time to onset was available in 190 of the 211 cases and ranged from 0 to 149 days with a median TTO of 13 days after 2nd dose. Time to onset by 14 days, 21 days and 42 days is presented in Table 130.

The majority of the 211 case reports of TTS following second dose occurred in male vaccinees (133, 63%). Of the 211 case reports of TTS following second dose, 77 were female (36%), and gender was unknown in 1 report. The age range of vaccinees was from 23 – 95 years, age was not provided in 17 of the 211 reports. Median age was 67 years and 166 (86%) of the reports were in vaccinees > 50 years. Outcome in 77 cases were reported as Not recovered, 11 Recovered, 67 Recovering, 18 Fatal, 7 Recovered with sequalae and Unknown in 31 report.

These events included the following sites of thrombosis (≥ 5): Pulmonary embolism (109), Deep vein thrombosis (60), Thrombosis (32), Cerebral venous sinus thrombosis (13), Cerebrovascular accident (12), Embolism (10), Thrombosis with thrombocytopenia syndrome (10) and Portal vein thrombosis (6).

In 48 out of 211 reports (23%) with Dose 2, there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms). The reported events (>2) included: Haemorrhage (10), Immune thrombocytopenia (10), Contusion (8), Cerebral haemorrhage (7), Haemoptysis (4), and Petechiae (3). There were two case report with the co-reported events from the HLT: Coagulopathies following Dose 2 with the event Coagulopathy (1) and Antiphospholipid syndrome (1). Pulmonary embolism (109/211, 52%) was the most common event.

Using the estimated exposure of 66536921 administered 2nd vaccinations with COVID-19 VACCINE ASTRAZENECA in EEA, UK, Philippines, Canada, and Australia the reporting rate of thrombotic events in combination with thrombocytopenia (with time to onset ≤ 21 days; 132 reports) following the second COVID-19 VACCINE ASTRAZENECA was estimated to be 1.98 per million doses. The majority of the vaccines who experienced TTS post Dose 2 were male (63%) and were older in age with a median age of 67 years. The rate of TTS following 2nd of COVID-19 VACCINE ASTRAZENECA is less compared to the

background rate for all age groups (See Table 132 and Table 133) of 5.62 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.75 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm [with updated OHDSI aligned codelists and washout periods]).

This rate of thrombotic events in combination with thrombocytopenia following 2nd dose of COVID-19 VACCINE ASTRAZENECA is below the estimated reporting rate of 14.42 per million doses for first dose of COVID 19 VACCINE ASTRAZENECA (1179 identified reports with time to onset ≤ 21 days; estimated exposure 81734351 administered doses). TTS events following the second dose had a different demographic pattern as well, being older and more likely male compared to dose 1.

Summary and conclusion for TTS is presented below after discussion of CVST+ thrombocytopenia.

Literature

Articles were reviewed to understand the pathophysiology of TTS (Mechanism of action of TTS) in association with the COVID-19 VACCINE ASTRAZENECA. Below is a brief discussion of the relevant articles.

- Baker et al 2021 sought to determine whether PF-4 can bind to COVID-19 VACCINE ASTRAZENCA or purified ChAdOx1 and begin to elucidate the nature of the interaction. The data established that PF-4 is capable of binding to ChAdOx1, the adenoviral vector utilized to deliver spike protein as part of COVID-19 VACCINE ASTRAZENECA. Clinically, thrombotic events following vaccination with COVID-19 VACCINE ASTRAZENECA have been associated with increased levels of anti-PF-4 antibodies. It has been hypothesized that PF-4-ChAdOx1 aggregates form, perhaps acting as an immune complex leading to development of anti-PF-4 antibody in pre-disposed individuals.

- Greinacher et al 2021 (Blood), suggests that COVID-19 VACCINE ASTRAZENECA, either ChAdOx1 or proteins present in the vaccine preparation, can bind with PF-4 forming immune complexes. The authors suggest that these complexes can drive a B-cell response resulting in high-titer anti-PF-4 antibodies, resulting in TTS. They hypothesize that EDTA present in the vaccine preparation could contribute to the breakdown of the endothelial barrier, allowing vaccine entry into the bloodstream, and that HEK293 cell proteins might result in auto-antibody production.

- Greinacher et al 2021 (NEJM), suggested that Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune

heparin-induced thrombocytopenia. Blood samples of 28 patients with TTS were analysed. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immunoglobulin (10 mg per milliliter).

- Bourguignon et al 2021, suggested that in the case of patients with autoimmune HIT and in patients with TTS, the inhibition of serum-induced platelet activating properties by IVIG was associated with increased platelet counts.

AstraZeneca Comment: The above 4 articles provide potential hypotheses for mechanism of TTS with COVID-19 VACCINE ASTRAZENECA; however these hypotheses have not been confirmed. Further evaluation is required to better characterize and confirm the mechanism of TTS with COVID-19 VACCINE ASTRAZENECA.

16.3.2.1.1 CVST with thrombocytopenia

Of the 2059 thrombosis with thrombocytopenia case reports reviewed cumulatively, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 522 (25%) cases. Of these 522 cases, 63% were in females, 37% occurred in males, and in 1% gender was unknown.

In 147 of the 522 (28%) of the CVST with Thrombocytopenia cases were fatal. CVST with thrombocytopenia cases by age group/gender/dose and fatality are provided in Table 145.

Table 145 Cerebral venous sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
All doses				
Age - 18-29 Yrs	37 (7)	41 (10)	0 (0)	78 (17)
Age - 30-39 Yrs	56 (20)	32 (13)	0 (0)	88 (33)
Age - 40-49 Yrs	88 (28)	36 (7)	0 (0)	124 (35)
Age - 50-59 Yrs	60 (15)	37 (11)	0 (0)	97 (26)
Age - 60-69 Yrs	61 (16)	27 (7)	0 (0)	88 (23)
Age - 70-79 Yrs	9 (4)	4 (1)	0 (0)	13 (5)
Age - 80+ Yrs	2 (0)	4 (0)	0 (0)	6 (0)
Age Unknown	13 (3)	11 (3)	4 (2)	28 (8)
Grand Total	326 (93)	192 (52)	4 (2)	522 (147)
Dose 1				
Age - 18-29 Yrs	37 (7)	41 (10)	0 (0)	78 (17)

Table 145 Cerebral venous sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
Age - 30-39 Yrs	56 (20)	32 (13)	0 (0)	88 (33)
Age - 40-49 Yrs	85 (27)	29 (7)	0 (0)	114 (34)
Age - 50-59 Yrs	59 (15)	35 (10)	0 (0)	94 (25)
Age - 60-69 Yrs	61 (16)	24 (7)	0 (0)	85 (23)
Age - 70-79 Yrs	9 (4)	3 (0)	0 (0)	12 (4)
Age - 80+ Yrs	1 (0)	4 (0)	0 (0)	5 (0)
Age Unknown	12 (3)	10 (3)	4 (2)	26 (8)
Grand Total	320 (92)	178 (50)	4 (2)	502 (144)
Dose 2				
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	0 (0)
Age - 30-39 Yrs	0 (0)	0 (0)	0 (0)	0 (0)
Age - 40-49 Yrs	3 (1)	7 (0)	0 (0)	10 (1)
Age - 50-59 Yrs	1 (0)	2 (1)	0 (0)	3 (1)
Age - 60-69 Yrs	0 (0)	3 (0)	0 (0)	3 (0)
Age - 70-79 Yrs	0 (0)	1 (1)	0 (0)	1 (1)
Age - 80+ Yrs	1 (0)	0 (0)	0 (0)	1 (0)
Age Unknown	1 (0)	1 (0)	0 (0)	2 (0)
Grand Total	6 (1)	14 (2)	0 (0)	20 (3)

N Number, yrs Years.

Reporting rate for CVST in combination with thrombocytopenia across age groups based on the data from the UK and EEA by risk window of 21 days and 42 days provided in Table 146 and Table 147 respectively; reporting rate is also stratified by Dose 1 and Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the UK was higher across the age groups when compared to the background rate except for reports in vaccinees aged >65 years (risk window 21 days) and > 50 years (risk window 42 days) with Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the EEA was higher when compared to the background rate in vaccinees aged < 70 years with all doses. In the EEA the reporting rate of CVST in combination with thrombocytopenia with Dose 2 was higher than the background rate for vaccinees aged < 49 years, however reporting rate in age group > 50 years was less compared to the background rate.

The observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented in Table 148. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS.

Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded). The results of the observed versus expected analyses suggests that observed cases of CVST with thrombocytopenia are more than expected for all age stratifications.

Table 146 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 21 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
All doses (UK)								
Age - 18-39 Yrs	6005301	41	37	6.83	6.16	0.1	6.73	6.06
Age - 40-49 Yrs	10195312	55	47	5.39	4.61	0.1	5.29	4.51
Age - 50-64 Yrs	18891602	55	52	2.91	2.75	0.2	2.71	2.55
Age - > 65 Yrs	13760415	7	7	0.51	0.51	0.2	0.31	0.31
Age Unknown	167800	8	6	47.68	35.76	-	-	35.76
Grand Total	49020430	166	149	3.39	3.04	0.1	3.29	2.94
Dose 1 (UK)								
Age - 18-39 Yrs	3067234	41	37	13.37	12.06	0.1	13.27	11.96
Age - 40-49 Yrs	5170940	52	45	10.06	8.7	0.1	9.96	8.6
Age - 50-64 Yrs	9521965	52	50	5.46	5.25	0.2	5.26	5.05
Age - > 65 Yrs	6932257	6	6	0.87	0.87	0.2	0.67	0.67
Age Unknown	111055	7	5	63.03	45.02	-	-	45.02
Grand Total	24803451	158	143	6.37	5.77	0.1	6.27	5.67
Dose 2 (UK)								
Age - 18-39 Yrs	2933789	0	0	0	0	0.1	-0.1	-0.1
Age - 40-49 Yrs	5018787	3	2	0.6	0.4	0.1	0.5	0.3
Age - 50-64 Yrs	9354376	3	2	0.32	0.21	0.2	0.12	0.01
Age - > 65 Yrs	6804552	1	1	0.15	0.15	0.2	-0.05	-0.05
Age Unknown	56622	1	1	17.66	17.66	-	-	-

Table 146 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 21 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
Grand Total	24168126	8	6	0.33	0.25	0.1	0.23	0.15
All doses (EEA)								
Age - 18-49 Yrs	11513485	95	58	8.25	5.04	0.07	8.18	4.97
Age - 50-59 Yrs	6275981	19	12	3.03	1.91	0.16	2.87	1.75
Age - 60-69 Yrs	18684704	41	24	2.19	1.28	0.4	1.79	0.88
Age - 70-79 Yrs	8010180	3	1	0.37	0.12	0.47	-0.1	-0.35
Age - 80+ Yrs	1094043	2	0	1.83	0	0	-	-
Age Unknown	7637	2	1	261.88	130.94	-	-	-
Grand Total	45586030	162	96	3.55	2.11	0.14	3.41	1.97
Dose 1 (EEA)								
Age - 18-49 Yrs	6274541	92	57	14.66	9.08	0.07	14.59	9.01
Age - 50-59 Yrs	3406841	19	12	5.58	3.52	0.16	5.42	3.36
Age - 60-69 Yrs	9600344	39	24	4.06	2.5	0.4	3.66	2.1
Age - 70-79 Yrs	4084682	3	1	0.73	0.24	0.47	0.26	-0.23
Age - 80+ Yrs	559647	2	0	3.57	0	0	3.57	0
Age Unknown	3956	2	1	505.56	252.78	-	-	-
Grand Total	23930011	157	95	6.56	3.97	0.14	6.42	3.83
Dose 2 (EEA)								
Age - 18-49 Yrs	5236563	3	1	0.57	0.19	0.07	0.5	0.12
Age - 50-59 Yrs	2867674	0	0	0	0	0.16	-0.16	-0.16

Table 146 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 21 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
Age - 60-69 Yrs	9082233	2	0	0.22	0	0.4	-0.18	-0.4
Age - 70-79 Yrs	3923679	0	0	0	0	0.47	-0.47	-0.47
Age - 80+ Yrs	533368	0	0	0	0	-	-	-
Age Unknown	3681	0	0	0	0	-	-	-
Grand Total	21647198	5	1	0.23	0.05	0.14	0.09	-0.09

[a] Background event rates per 1M PY per 21 days from Truven Market Scan-2019.

CVST Cerebral Venous Sinus Thrombosis, EEA European Economic Area, PY Person Years, UK United Kingdom, yrs Years.

Table 147 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 42 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
All doses (UK)								
Age - 18-39 Yrs	6005301	43	38	7.16	6.33	0.2	6.96	6.13
Age - 40-49 Yrs	10195312	59	50	5.79	4.9	0.2	5.59	4.7
Age - 50-64 Yrs	18891602	60	57	3.18	3.02	0.4	2.78	2.62
Age - > 65 Yrs	13760415	10	9	0.73	0.65	0.4	0.33	0.25
Age Unknown	167800	10	8	59.59	47.68	0	-	-
Grand Total	49020430	182	162	3.71	3.3	0.2	3.51	3.1

Table 147 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 42 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
Dose 1 (UK)								
Age - 18-39 Yrs	3067234	43	38	14.02	12.39	0.2	13.82	12.19
Age - 40-49 Yrs	5170940	56	48	10.83	9.28	0.2	10.63	9.08
Age - 50-64 Yrs	9521965	57	55	5.99	5.78	0.4	5.59	5.38
Age - > 65 Yrs	6932257	9	8	1.3	1.15	0.4	0.9	0.75
Age Unknown	111055	8	6	72.04	54.03	0	-	-
Grand Total	24803451	173	155	6.97	6.25	0.2	6.77	6.05
Dose 2 (UK)								
Age - 18-39 Yrs	2933789	0	0	0	0	0.2	-0.2	-0.2
Age - 40-49 Yrs	5018787	3	2	0.6	0.4	0.2	0.4	0.2
Age - 50-64 Yrs	9354376	3	2	0.32	0.21	0.4	-0.08	-0.19
Age - > 65 Yrs	6804552	1	1	0.15	0.15	0.4	-0.25	-0.25
Age Unknown	56622	2	2	35.32	35.32	0	-	-
Grand Total	24168126	9	7	0.37	0.29	0.2	0.17	0.09
All doses (EEA)								
Age - 18-49 Yrs	11513485	101	58	8.77	5.04	0.14	8.63	4.9
Age - 50-59 Yrs	6275981	21	12	3.35	1.91	0.32	3.03	1.59
Age - 60-69 Yrs	18684704	45	26	2.41	1.39	0.8	1.61	0.59
Age - 70-79 Yrs	8010180	4	1	0.5	0.12	0.94	-0.44	-0.82
Age - 80+ Yrs	1094043	2	0	1.83	0	0	-	-
Age Unknown	7637	2	1	261.88	130.94	-	-	-

Table 147 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

Age Group	Total Exposed (in million)	Cases within Risk Window of 42 days	By Confirmed, probable and possible cases	Reporting Rate (per million)	Reporting Rate (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for confirmed probable and possible
Grand Total	45586030	175	98	3.84	2.15	0.28	3.56	1.87
Dose 1 (EEA)								
Age - 18-49 Yrs	6274541	98	57	15.62	9.08	0.14	15.48	8.94
Age - 50-59 Yrs	3406841	21	12	6.16	3.52	0.32	5.84	3.2
Age - 60-69 Yrs	9600344	43	26	4.48	2.71	0.8	3.68	1.91
Age - 70-79 Yrs	4084682	4	1	0.98	0.24	0.94	0.04	-0.7
Age - 80+ Yrs	559647	2	0	3.57	0	0	-	-
Age Unknown	3956	2	1	505.56	252.78	-	-	-
Grand Total	23930011	170	97	7.1	4.05	0.28	6.82	3.77
Dose 2 (EEA)								
Age - 18-49 Yrs	5236563	3	1	0.57	0.19	0.14	0.43	0.05
Age - 50-59 Yrs	2867674	0	0	0	0	0.32	-	-
Age - 60-69 Yrs	9082233	2	0	0.22	0	0.8	-0.58	-0.8
Age - 70-79 Yrs	3923679	0	0	0	0	0.94	-	-
Age - 80+ Yrs	533368	0	0	0	0	0	-	-
Age Unknown	3681	0	0	0	0	-	-	-
Grand Total	21647198	5	2	0.23	0.09	0.28	-0.05	-0.23

[a] Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CVST, Cerebral Venous Sinus Thrombosis; EEA, European Economic Area; PY, Person Years; UK, United Kingdom, yrs Years.

Table 148 Observed versus Expected Analysis for CVST+TCP

AEs	Risk window[a]	Background rates[b]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
CVST+TCP - Overall (Global)	14	0.25	291626957	331	27.95	11.84 (10.6 - 13.19)	Observed significantly > expected
CVST+TCP - Overall (Global)	21	0.25	291626957	394	41.92	9.4 (8.49 - 10.37)	Observed significantly > expected
CVST+TCP - Overall (Global)	42	0.25	291626957	424	83.84	5.06 (4.59 - 5.56)	Observed significantly > expected
CVST+TCP - Overall (Global) (including cases with unknown time to onset)	14	0.25	291626957	425	27.95	15.21 (13.79 - 16.72)	Observed significantly > expected
CVST+TCP - Overall (Global) (including cases with unknown time to onset)	21	0.25	291626957	488	41.92	11.64 (10.63 - 12.72)	Observed significantly > expected
CVST+TCP - Overall (Global) (including cases with unknown time to onset)	42	0.25	291626957	518	83.84	6.18 (5.66 - 6.73)	Observed significantly > expected
Observed versus Expected Analysis for CVST+TCP by age group (EU/UK)							
CVST+TCP 18 to 49	14	0.17	27716022	166	1.81	91.71 (78.29 - 106.77)	Observed significantly > expected
CVST+TCP 50 to 59	14	0.39	19552392	46	2.92	15.75 (11.53 - 21.01)	Observed significantly > expected
CVST+TCP 60 to 69	14	0.33	28510714	47	3.61	13.02 (9.57 - 17.31)	Observed significantly > expected

Table 148 Observed versus Expected Analysis for CVST+TCP

AEs	Risk window[a]	Background rates[b]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
CVST+TCP 70 to 79	14	0.38	14795684	3	2.16	1.39 (0.29 - 4.06)	Observed > expected
CVST+TCP 18 to 49	21	0.17	27716022	191	2.71	70.48 (60.84 - 81.21)	Observed significantly > expected
CVST+TCP 50 to 59	21	0.39	19552392	63	4.38	14.38 (11.05 - 18.4)	Observed significantly > expected
CVST+TCP 60 to 69	21	0.33	28510714	57	5.41	10.54 (7.98 - 13.65)	Observed significantly > expected
CVST+TCP 70 to 79	21	0.38	14795684	6	3.23	1.86 (0.68 - 4.04)	Observed > expected
CVST+TCP 18 to 49	42	0.17	27716022	203	5.42	37.45 (32.48 - 42.98)	Observed significantly > expected
CVST+TCP 50 to 59	42	0.39	19552392	68	8.77	7.75 (6.02 - 9.83)	Observed significantly > expected
CVST+TCP 60 to 69	42	0.33	28510714	66	10.82	6.1 (4.72 - 7.76)	Observed significantly > expected
CVST+TCP 70 to 79	42	0.38	14795684	7	6.47	1.08 (0.43 - 2.23)	Observed > expected

[a] Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CI, Confidence Interval; CVST, Cerebral Venous Sinus Thrombosis; E, Expected; O, Observed; TCP, Thrombocytopenia

Summary

The analysis of thrombosis in combination with thrombocytopenia following the second dose showed that the rate of events was extremely low following the second dose of COVID-19 VACCINE ASTRAZENECA and lower than after administration of the first dose. The majority of the vaccinees who experienced TTS events post dose 2 were male (63% vs 45%) and were older (PPD) compared to first dose recipients. The median time to onset was similar (13 days vs 12 days.

Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism and Thrombosis.

Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-three percent of the fatal report occurred with 14 days compare to 64% for all cases and 88% of the fatal report occurred within 21 days compare to 80% for all cases The highest number of fatal reports (49%) occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event. The total number and percent of fatal reports since April 2021 are decreasing compared to January 2021-March 2021. There is an increased fatality rate in December; however, only 10 cases were reported in this month received which could explain the sharp increase in the percentages.

The arterial events were reported highest in the age group of 50-59 and 60-69. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous was equally distributed in age group 30-39,40-49,50-59 and 60-69 and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age group of 40-49, 50-59 and 60 – 69 years.. The occurrence in female was higher than in the male.

The highest number of cases were reported from UK (49%) while it received 49.02 million doses of the total worldwide doses.

The most common confounding factors in descending order of frequency in all 2060 cases were autoimmune conditions, malignancy, past history of heparin, obesity and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were past history of heparin use and malignancy. The dates of heparin administered were not reported in all cases.

The study by Baker et al 2021 shows an interaction between the ChAdOx1 vaccine vector used in COVID-19 Vaccine AstraZeneca and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (Blood) suggested that ChAdOx1 itself or proteins contained

within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS.

Conclusion:

From the data identified during the reporting period and also taking into account the cumulative experience, no updates to the COVID-19 VACCINE ASTRAZENECA CDS or RMP.

Thrombosis in combination with thrombocytopenia/TTS is contained in Section 4.4 (Special warnings and special precautions for use) in the COVID-19 VACCINE ASTRAZENECA CDS. In addition, COVID-19 VACCINE ASTRAZENECA is contraindicated (CDS Section 4.3) for use in any persons who have experienced thrombosis in combination with thrombocyopenia with any Covid-19 vaccine. Finally, thrombosis in combination with thrombocytopenia/ TTS is listed as an Important Identified Risk in the Core and EU RMPs for COVID-19 VACCINE ASTRAZENECA. As such, the topic will continue to be kept under close surveillance by AstraZeneca.

More detailed information regarding this Important identified risk is provided in Section 16.4.1.1.

16.3.3 New information on other potential risks not categorised as important

The AESIs for COVID-19 VACCINE ASTRAZENECA and associated PTs are listed in Appendix 7.

AESIs listed in Appendix 7 for COVID-19 VACCINE ASTRAZENECA have been included for review in Section 16.3 of this PSUR (Safety concerns in the COVID-19 VACCINE ASTRAZENECA RMP) and Appendix 8 (O/E Analyses). Section 16.3.3.1 below includes a review of Pregnancy – Neonatal outcomes as an AESI not included elsewhere in this PSUR. Discussions of any trends, signals, or updates to labels and RMP are contained within these respective sections of this PSUR document.

16.3.3.1 Pregnancy - Neonatal Outcomes:

In order to appropriately assess all cases reported to the company with any congenital anomaly or adverse neonatal outcome, a search cumulatively and during the reporting period of this PBRER was done with the following PTs: " Acrocephalosyndactyly; Amniotic band syndrome; Anencephaly; Annular pancreas; Anomalous pulmonary venous connection; Anophthalmos; Anorectal malformation; Anotia; Aorticopulmonary septal defect; Arnold-Chiari malformation; Arteriovenous malformation; Atrial septal defect; Atrioventricular septal defect; Auditory neuropathy spectrum disorder; Brain malformation; Breast malformation; Cardiac septal defect; Cataract congenital; Cerebral arteriovenous malformation haemorrhagic; Cerebral cavernous malformation; Cerebrovascular arteriovenous malformation; Choanal atresia; Cleft lip; Cleft lip and palate; Cleft palate; Cloacal exstrophy;

Coarctation of the aorta; Congenital absence of bile ducts; Congenital aortic valve stenosis; Congenital arterial malformation; Congenital cerebral haemangioma; Congenital coronary artery malformation; Congenital cystic kidney disease; Congenital diaphragmatic hernia; Congenital ectopic bladder; Congenital eye disorder; Congenital eyelid malformation; Congenital foot malformation; Congenital genital malformation; Congenital genital malformation female; Congenital genital malformation male; Congenital hand malformation; Congenital hearing disorder; Congenital heart valve disorder; Congenital heart valve incompetence; Congenital hydrocephalus; Congenital hydronephrosis; Congenital intestinal malformation; Congenital jaw malformation; Congenital joint malformation; Congenital large intestinal atresia; Congenital lymphoedema; Congenital megacolon; Congenital mitral valve incompetence; Congenital mitral valve stenosis; Congenital nose malformation; Congenital oesophageal stenosis; Congenital oral malformation; Congenital pulmonary artery anomaly; Congenital pulmonary valve atresia; Congenital rubella infection; Congenital rubella syndrome; Congenital skin disorder; Congenital small intestinal atresia; Congenital syphilis; Congenital tricuspid valve atresia; Congenital vesicoureteric reflux; Conjoined twins; Constricted ear deformity; Craniorachischisis; Craniosynostosis; Cryptorchism; Cystic lymphangioma; Deaf mutism; Deafness congenital; Death neonatal; Developmental glaucoma; Developmental hip dysplasia; Double outlet right ventricle; Duodenal atresia; Dysmorphism; Ear malformation; Ebstein's anomaly; Encephalocele; Epispadias; Exomphalos; Fallot's tetralogy; Foetal alcohol syndrome; Foetal anticonvulsant syndrome; Foetal distress syndrome; Foetal growth restriction; Foetal malformation; Gastrointestinal arteriovenous malformation; Gastrointestinal malformation; Gastroschisis; Genitalia external ambiguous; Haemangioma congenital; Haemangioma of retina; Haemorrhagic arteriovenous malformation; Hepatic arteriovenous malformation; Heterotaxia; Holoprosencephaly; Hydrops foetalis; Hypoplastic left heart syndrome; Hypoplastic right heart syndrome; Hypospadias; Iniencephaly; Interruption of aortic arch; Intestinal atresia; Kidney malformation; Limb malformation; Limb reduction defect; Lissencephaly; Low birth weight baby; Malformation biliary; Malformation venous; Microcephaly; Microencephaly; Microphthalmos; Microtia; Mitral valve atresia; Mitral valve hypoplasia; Multiple gastrointestinal atresias; Neural tube defect; Oesophageal atresia; Parachute mitral valve; Patent ductus arteriosus; Polydactyly; Porencephaly; Premature baby; Pulmonary aplasia; Pulmonary artery atresia; Pulmonary artery stenosis congenital; Pulmonary malformation; Pulmonary valve stenosis congenital; Pyloric stenosis; Rectal atresia; Renal aplasia; Renal arteriovenous malformation; Renal dysplasia; Renal failure neonatal; Renal hypoplasia; Respiratory tract malformation; Retinal arteriovenous malformation; Schizencephaly; Skeletal dysplasia; Skin malformation; Skull malformation; Spina bifida; Spina bifida cystica; Spina bifida occulta; Spine malformation; Spleen malformation; Stillbirth; Syndactyly; Talipes; Thyroid malformation; Tracheo-oesophageal fistula; Transposition of the great vessels; Truncus arteriosus persistent; Umbilical malformation; Univentricular heart; Urethral valves; Urinary tract malformation; VACTERL syndrome; Vascular malformation; Vein of Galen

aneurysmal malformation; Venolymphatic malformation; Ventricular septal defect; Vallecular cyst; Foetal vascular malperfusion".

Cumulatively, 85 cases reporting any PTs (outlined above) from the concept of Pregnancy outcomes-Neonates were reported since launch until the DLP of this PBRER. Upon further review, 41 of these cases were acquired conditions and/or presented in elderly age or adults and not congenital malformations and hence not included for further review.

During the reporting period of this PBRER until 28 December 2021, 66 cases were reported among this concept of pregnancy outcomes_Neonates, upon further review only 38 cases were reported among neonatal age or where linked to a neonate or a pregnancy product, therefore included in this section. Among these, there were 2 cases of abortions, 15 congenital anomalies, 1 case of decreased foetal motility, 4 cases of lower weight for gestational age, one case of perinatal stroke, 8 cases of prematurity, one case of retardation of neonatal growth, and 6 cases of stillbirth. Some cases of these section may be described in section regarding Use of COVID-19 VACCINE ASTRAZENECA in pregnant women (Section 16.3.5.1.1). The cases reported during this interval are described below:

Abortion

PPD **:** A PPD-year-old vaccinee, got a first dose of COVID 19 vaccine AstraZeneca at unknown time of PPD The vaccinee experienced PPD abortion. No more information on this case.

AstraZeneca Comment: Due to limited information on exact circumstances leading to the event, risk factors leading to the event (PPD), concomitant medications, concurrent diseases, detailed etiological and diagnostic workup (imaging tests), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** A PPD-year-old who experienced PPD , 29 days after vaccination with the second dose in the PPD . On an unknown date, the patient experienced PPD

AstraZeneca Comment: Due to limited information on detailed baseline health condition before vaccination, circumstances leading to the event, relevant medical history (diabetes, PPD , infections, thyroid disorders), family history, concomitant medication, risk factors (PPD), lifestyle, detailed etiological and diagnostic workup (pelvic exam, chromosomal tests, complete blood count),the evaluation did not find evidence to suggest a causal relationship between the event and COVID-19 VACCINE ASTRAZENECA.

Congenital Anomalies:

PPD **:** A spontaneous report has been received from the regulatory authority in PPD (EMA) via consumer concerning a PPD patient neonate. No medical history was reported. No concomitant products were reported. The patient received *COVID-19 VACCINE ASTRAZENECA* on PPD . On PPD , the patient's PPD reported a finding of PPD took the first dose of the AstraZeneca vaccine when PPD . (preferred term: PPD).

AstraZeneca Comment: Due to limited information on the further clarification of the event, circumstances leading to the event, relevant medical and family history of the patient, concurrent diseases and medications, final outcome of the event, risk factors, etiological and complete diagnostic work-up (physical examination, full diagnostic laboratory panel), the evaluation did not find evidence to suggest a causal relationship between reported event and the vaccine COVID-19 VACCINE ASTRAZENECA.

PPD **:** A neonate born to PPD of unknown age died on PPD due to PPD received *COVID-19 VACCINE ASTRAZENECA*. PPD received vaccine PPD Concomitant medication reported includes PPD

AstraZeneca Comment: The cause of death was PPD *. Death occurred seventy-four days after the date of vaccination. Due to limited information on last menstruation date of the mother, event onset dates, additional medical history and family history of* PPD *, details of* PPD *screening tests during pre and post vaccination (Alpha fetoprotein, human chorionic gonadotropin, estriol, inhibin A), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.*

PPD **:** A PPD -year-old vaccinee with a history of PPD received the first dose on PPD . Concomitant medications included PPD On an unknown date, foetal cardiac ultrasound scan diagnosed PPD . At the time of reporting, the outcome of the event of PPD was ongoing or not recovered.

AstraZeneca Comment: This case report concerns PPD *-year-old* PPD *vaccinee who had exposure to COVID-19 VACCINE ASTRAZENECA* PPD *(preferred term: Maternal exposure during pregnancy) and* PPD *experienced event of* PPD *. Due to limited information on baseline health condition before vaccination, relevant medical history, concurrent diseases, concomitant medications, date of vaccination, event onset date(*PPD *exposure during pregnancy), event outcome, detailed diagnostic and etiologic workup (gynaecological examination,* PPD *l imaging morphology,*

amniocentesis), the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between event and COVID-19 VACCINE ASTRAZENECA.

PPD: A PPD of unknown gender whose PPD-year-old PPD received *COVID-19 VACCINE ASTRAZENECA* on PPD. On an unknown date in PPD The PPD died on PPD. It is not known whether an autopsy was performed. The cause of death was PPD

AstraZeneca Comment: Due to limited information on exact circumstances leading to the events, complete course of pregnancy, baseline health condition before COVID-19 VACCINE ASTRAZENECA administration, concomitant medications, medical history, concurrent conditions, risk factors (PPD conditions of rubella, diabetes, PPD), detailed etiological and diagnostic workup (complete diagnostic profile, infection profile, relevant imaging studies, genetic assay) the evaluation did not find evidence to suggest a causal relationship between the events and vaccine COVID-19 VACCINE ASTRAZENECA.

PPD: A spontaneous report regarding a neonate was received from a consumer. No medical history was reported. PPD had PPD years with no significant medical history and received *COVID-19 VACCINE ASTRAZENECA* (Dose 1, batch number ABW2953), on PPD. On PPD, the patient (neonate) experienced PPD The dates when these events started where not reported, the events were considered serious due to congenital anomaly.

AstraZeneca Comment: Due to limited information on relevant medical and family history, circumstances leading to the events, other risk factors (PPD and chronic conditions, PPD, concomitant medications and vaccination history, detailed diagnostic and etiologic workup (ultrasound, blood tests), gestational age at date of COVID-19 VACCINE ASTRAZENECA administration, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD PPD: Spontaneous report received from a physician via the regulatory authority in PPD concerning a PPD patient of Unknown ethnic origin. Concomitant medication included PPD. On an unknown date, the patient received *COVID-19 VACCINE ASTRAZENECA*. Patient was PPD. On PPD, the patient experienced

PPD

Patient queried whether this was related to recent COVID vaccine PPD

AstraZeneca Comment: This case concerns a PPD -year-old PPD with reported event PPD exposure during pregnancy in association with COVID-19 VACCINE ASTRAZENECA. Due to limited information on baseline health condition before vaccination, relevant medical history, concurrent diseases, concomitant medications, date of vaccination, event onset date(foetal exposure during pregnancy), event outcome, detailed diagnostic and etiologic workup (gynaecologial examination, fetal imaging morphology, PPD), the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between event and COVID-19 VACCINE ASTRAZENECA.

PPD **:** A PPD year-old PPD received the 1st dose of COVID-19 VACCINE ASTRAZENECA on an unknown date. On PPD , Patient was required to PPD

Patient has PPD Patient was PPD

AstraZeneca Comment: This case concerns a PPD -year-old PPD with reported event foetal exposure during pregnancy in association with COVID-19 VACCINE ASTRAZENECA. Due to limited information on baseline health condition before vaccination, relevant medical history, concurrent diseases, concomitant medications, date of vaccination, event onset date(foetal exposure during pregnancy), event outcome, detailed diagnostic and etiologic workup (gynaecological examination, foetal imaging morphology, PPD), the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between event and COVID-19 VACCINE ASTRAZENECA.

PPD **:** A spontaneous report has been received from the consumer. On PPD the PPD of the patient received first dose of *COVID-19 VACCINE ASTRAZENECA*. On an unknown date, the patient experienced PPD . The PPD of the patient was exposed to the vaccine on the PPD

AstraZeneca Comment: Due to limited information on exact circumstances leading to the event, onset date of the event, risk factors leading to the event, family history, concurrent condition concomitant medications, detailed etiological and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between events and COVID-19 VACCINE ASTRAZENECA.

PPD: A spontaneous report was received from the regulatory authority in PPD (EMA) via Consumer concerning a PPD-old PPD patient of unknown ethnic origin. The patient was born to a PPD-year-old PPD. No medical history and no concomitant products were reported. The patient received Dose 1 of *COVID-19 VACCINE ASTRAZENECA* via transplacental route on PPD and Dose 2 of *COVID-19 VACCINE ASTRAZENECA* via transplacental route on PPD. On PPD, at PPD of gestation age, the patient experienced PPD. The patient died after 4 days. The cause of death was PPD. It was not known whether an autopsy was performed.

AstraZeneca Comment: Due to limited information on the details and circumstances leading to the events, maternal and paternal medical history, prenatal check-up (was it regularly and properly followed) and congenital screening, maternal exposure to other drugs and possible illnesses during pregnancy, family history, etiological and diagnostic workup (chest Xray, electrocardiogram, echocardiogram, complete blood count, metabolic panel), autopsy report, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD: A spontaneous report has been received from the regulatory authority in PPD via consumer concerning a neonate. Family history included PPD. The parent treatment history included PPD, *COVID-19 VACCINE ASTRAZENECA* on PPD and booster with the same vaccine on PPD. On PPD, the patient (neonate) presented birth defects (preferred term: Congenital anomaly). PPD was reported among exams performed to the neonate.

AstraZeneca Comment: The events could be in association with each other. Parent history of PPD *could be considered as a risk factor for the event* PPD*. Due to limited information on other risk factors (folate deficiency, family history of* PPD*), concomitant medications, etiological and diagnostic work up (obstetric and pediatric assessment, complete blood analysis with diabetic profile and vitamin dosage), the evaluation did not find evidence to suggest a causal relationship between the events and vaccine COVID-19 VACCINE ASTRAZENECA.*

PPD: PPD patient of PPD years old, PPD, with a medical history of PPD treated PPD. On PPD received first dose of *COVID-19 VACCINE ASTRAZENECA*, the following day PPD experienced high fever, nausea and fatigue. Per the information reported to the company, the patient was PPD when PPD got the vaccine or PPD one week after having the vaccine. At PPD

PPD which did not found any genetic or chromosomal cause confirmed by the medicinal fetal unit. The PPD was considered uncomplicated. PPD had no other risk factors for PPD, had healthy BMI, do not have diabetes, PPD, do not take any of the medications known to increase risk and do not have any family history of neural tube defects. PPD had also been taking PPD for two months prior to conception. The symptoms PPD experienced within hours of having *COVID-19 VACCINE ASTRAZENECA* were PPD was particularly concerned that the high temperature and fever PPD experienced for 24 hours, at the PPD, may have contributed to cause the PPD. Case id PPD is the neonate report of this case.

AstraZeneca Comment: The reported event of High temperature could be contributory factor for PPD*. Due to limited information regarding details and circumstances surrounding the events, baseline health condition before vaccination, obstetric history, detailed medication history, medical history, risk factors (*PPD*), concurrent diseases, concomitant medications, etiological and diagnostic work up, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.*

PPD**:** PPD patient of PPD years old, PPD, with a medical history of PPD treated PPD On PPD, received first dose of COVID-19 Astrazeneca, the following day PPD, experienced high fever, nausea and fatigue. Per the information reported to the company, the patient was PPD when PPD got the vaccine, or PPD one week after having the vaccine. PPD which did not found any genetic or chromosomal cause confirmed by the medicinal fetal unit. The PPD was considered uncomplicated. PPD had no other risk factors for PPD , had healthy BMI, do not have diabetes, PPD, do not take any of the medications known to increase risk and do not have any family history of neural tube defects. PPD had also been taking PPD was particularly concerned that the high temperature and fever PPD experienced for 24 hours, at the PPD, may have contributed to cause the PPD. Case id PPD is the neonate report of this case.

AstraZeneca Comment: Due to limited information on circumstances leading to the events, clinical course, concurrent diseases (PPD), relevant medical and family history, concomitant medications(statins), specific risk factors, etiological and complete diagnostic workup (complete blood count, clinical examinations), the evaluation did not find evidence to suggest a causal relationship between events and AZD1222.

PPD **:** A spontaneous report received from the regulatory authority in PPD (EMA) via a consumer. The report concerns a PPD of unknown gender and ethnic origin. No medical history or concomitant medications were reported. The patient received Dose 2 of COVID-19 VACCINE ASTRAZENECA via transplacental route on PPD . On PPD was identified and the pregnancy ended as PPD

AstraZeneca Comment: The events may be in association with each other. The events occurred 147 days after vaccine administration. The cause of death was PPD . Due to limited information on circumstances leading to the events, risk factors, mothers concurrent diseases and concomitant medications, detailed etiological and diagnostic workup, autopsy results, the evaluation did not find evidence to suggest a causal relationship between the events and the vaccine COVID-19 VACCINE ASTRAZENECA.

PPD **:** A spontaneous report has been received from consumer via regulatory authority in PPD (EMA), concerning a PPD patient of unknown ethnic origin (age PPD years. No medical history and concomitant products were reported. On an unknown date, the patient received *COVID-19 VACCINE ASTRAZENECA*. On PPD , the patient received COVID-19 VACCINE MODERNA. On an unknown date, the PPD had had PPD and died at gestational Age PPD

AstraZeneca Comment: Due to limited information on baseline health condition before vaccination, relevant medical history, relevant family history, concurrent diseases, risk factors PPD and detailed diagnostic and etiologic workup (physical examination, blood laboratory tests, infection profile, gynaecological workup, endocrinological workup, medical imaging investigations), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** A spontaneous report has been received from the Regulatory Authority in PPD via Consumer concerning a PPD -year-old PPD patient. The patient's past medical history included PPD Concomitant medication included PPD The patient

received first dose of *COVID-19 VACCINE ASTRAZENECA* on PPD . The same day, the patient experienced PPD Patient was PPD when PPD was vaccinated with *COVID-19 VACCINE ASTRAZENECA*. 20 week ultrasound showed the PPD Foetal heart scan confirmed serious PPD Pregnancy was PPD

AstraZeneca Comment: Underlying current medical history included Hypothyroidism and Type 1 diabetes could be considered as contributory risk factors for the event. Due to limited information on circumstances leading to the events, complete pregnancy course, other relevant medical history, concomitant medications, family history, other risk factors and comorbidities (PPD) and complete etiologic or diagnostic work up (serum electrolyte levels, biochemical blood analysis, complete blood panel, thyroidal function tests, genetics testing results, gynaecology examination results), the evaluation did not find evidence to suggest a causal relationship between the event and vaccine COVID-19 VACCINE ASTRAZENECA.

Decreased foetal motility

PPD : A PPD year-old vaccinee experienced decreased foetal motility (PPD on the same day as vaccination, PPD . The outcome of pregnancy was unknown.

AstraZeneca Comment: The event could have been in association with the listed event of pyrexia. Due to limited information on event details including a detailed description of circumstances leading to the events, relevant medical history, family history, other concurrent conditions, other concomitant medications, diagnostic and etiological workup (physical exam, obstetric abdominal examination, assessment of the foetal heartbeat, full blood count, blood chemistry), risk factors, the evaluation did not find evidence to suggest a causal relationship between the event and COVID-19 VACCINE ASTRAZENECA.

Lower weight for gestational age

PPD **:** A spontaneous report has been received from the regulatory authority in PPD (EMA) via consumer concerning a PPD years old PPD patient of Unknown ethnic origin Patient was PPD when first vaccinated and no concomitant products were reported. The patient received *COVID-19 VACCINE ASTRAZENECA* on PPD . On PPD , the patient experience PPD 4 weeks after vaccination, at PPD with a weight of PPD kg.

AstraZeneca Comment: Both events could be considered related to each other. Due to limited information on the further clarification of the events, circumstances leading to them, patient`s baseline health status, relevant medical and family history of the patient, concurrent diseases, concomitant medications, risk factors (PPD), etiological and complete diagnostic work-up (physical examination, full diagnostic laboratory panel, computerized tomography scan of abdomen, gynaecological assessments), the evaluation did not find evidence to suggest a causal relationship between the events and the vaccine.

PPD : A pregnant PPD of unknown age received the vaccine at PPD . The neonate had not PPD The weight of neonate at birth was PPD .

AstraZeneca Comment: Due to limited information on relevant medical history, concomitant medication, comorbidities, event details including circumstances leading to the events, diagnostic and etiological workup, discussion on lifestyle and specific risk factors, the evaluation did not find evidence to suggest a causal relationship between the events and vaccine COVID-19 VACCINE ASTRAZENECA.

PPD : A spontaneous report has been received from the regulatory authority in PPD (EMA) via Consumer concerning a PPD years old PPD patient. No medical history was reported. No concomitant products were reported. The patient received *COVID-19 VACCINE ASTRAZENECA* on PPD . On PPD , the patient was vaccinated with COVID-19 VACCINE PFIZER/BIONTECH at PPD . On an unknown date, the patient experienced PPD . On PPD , the patient experienced PPD . The patient recovered with sequelae from the event(s) of PPD after 1 week on PPD .

AstraZeneca Comment: Due to limited information on relevant medical and family history, circumstances leading to the event, risk factors (PPD), concomitant medications and vaccination history, detailed diagnostic and etiologic workup (blood tests, urinalysis, ultrasound), the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between events and COVID-19 VACCINE ASTRAZENECA.

PPD : Consumer report concerning a PPD of unknown gender. PPD year-old PPD past medical history is PPD The PPD was vaccinated at PPD with COVID-19 VACCINE ASTRAZENECA. It was reported that during the pregnancy the PPD

AstraZeneca Comment: Due to limited information on pre vaccination health status of the patient, circumstances leading to the event, clinical course, relevant medical and family history , concurrent diseases (PPD ,other concomitant medications, detailed etiological and diagnostic workup (complete physical examination, complete blood count, infection panel, foetal monitoring, amniocentesis), the evaluation did not find evidence to exclude a reasonable possibility of a causal relationship between the event and COVID-19 VACCINE ASTRAZENECA.

Perinatal stroke:

PPD **:** A spontaneous report had been received from the regulatory authority in PPD via consumer. The report concerned a neonate of unknown gender of Unknown ethnic origin. The patient received *COVID-19 VACCINE ASTRAZENECA.* On PPD, the patient experienced perinatal stroke (preferred term: Perinatal stroke). On an unknown date, the patient experienced stroke (preferred term: PPD). On an unknown date, the patient experienced PPD. On an unknown date, the patient experienced PPD. The patient recovered with sequelae from the event(s) of perinatal stroke after 1 day on PPD. At the time of reporting, the event of stroke was ongoing. The result for the magnetic resonance imaging (MRI), echocardiogram, electroencephalogram (EEG) tests was unknown.

AstraZeneca Comment: The events Perinatal stroke, PPD *could be considered in association with each other. Due to limited information on the circumstances leading to the events, date of COVID-19 VACCINE ASTRAZENECA administration, perinatal risk factors* PPD *, relevant family history, underlying neonatal comorbidities (*PPD *), treatment, etiologic and diagnostic work up (complete physical and neurological examination of the neonate, complete blood count with infection panel, serum electrolytes and the official results of the magnetic resonance imaging (MRI), echocardiogram, electroencephalogram (EEG) done), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.*

Prematurity:

PPD: A solicited report had been received from a consumer, regarding a subject enrolled in study D8110C00003, COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER). The report concerned a male patient of PPD ethnic origin born in PPD. No medical history was reported. On PPD, the patient received *COVID-19 VACCINE ASTRAZENECA.* On PPD, the patient received second dose of *COVID-19*

VACCINE ASTRAZENECA. On an unknown date, the patient experienced PPD was in PPD . During PPD , the patient experienced PPD . On an unknown date, the patient experienced birth at gestational age PPD (preferred term: Premature baby).

AstraZeneca Comment: During PPD *approximately, a* PPD *received COVID-19 VACCINE ASTRAZENECA for prophylaxis. During the birth which was premature, the preterm neonatal was on* PPD *. Prematurity and* PPD *are not causally related to COVID-19 VACCINE ASTRAZENECA.*

PPD **:** Spontaneous report from the regulatory authority in PPD, concerning a PPD -year-old pregnant patient who received COVID-19 VACCINE ASTRAZENECA on PPD . The pregnancy was reported as a high-risk pregnancy where the patient was taking PPD . In addition, the patient was taking PPD The day of the vaccination patient felt heaviness of limbs, chills, generalized muscle aches, fatigue, headache, stomach pain and exhaustion, PPD recovered from all symptoms postvaccination one day after. It was reported that the patient had exposure to the vaccine apparently 3 months before conception and PPD On an unknown date the patient had PPD . The neonate was delivered PPD . The neonate besides prematurity does not have any other disease or condition, is otherwise healthy.

*AstraZeneca Comment: Due to limited information on events onset dates, baseline health condition of the patient before vaccination, family and medical history (*PPD *), risk factors (*PPD *), etiological and diagnostic workup (complete blood analysis, coagulation panel, urine analysis, infection panel, blood sugar levels, lipid profile, imaging studies), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.*

PPD **:** A male neonate whose PPD received the first dose of vaccine at PPD Eight days later, the PPD experienced PPD The baby died the next day. An autopsy was not performed.

AstraZeneca Comment: Due to limited information on circumstances leading to fatal outcome (Death neonatal), clinical course, cause of death, autopsy report, etiological and diagnostic workup, medical history of neonate's mother and the course of the pregnancy, the evaluation did not find evidence to suggest a causal relationship between the event and the vaccine COVID-19 VACCINE ASTRAZENECA 2. It is to be noted that due to limited data on use of the vaccine in pregnant women, as a precautionary measure, vaccination with COVID-19 VACCINE ASTRAZENECA is not recommended during pregnancy, and such use should be based on assessment of vaccination benefit versus any potential risks.

PPD: A PPD neonate whose PPD received the vaccine at PPD The same day as vaccination, the PPD of the neonate was diagnosed with PPD It did not resolve and PPD It was reported the baby has been healthy overall and was not diagnosed with any genetic or inherited disorder.

AstraZeneca Comment: Due to limited information on patient age, exact onset date of events reported, relevant medical and family history, circumstances leading to the events, weeks of pregnancy, risk factors (PPD), other concomitant medications and vaccination history, detailed diagnostic and etiologic workup (complete blood panel with infectious profile, ultrasound scans, echocardiogram, oxygen saturation, neonatologist opinion, neurological workup of the neonate), clarification regarding route of vaccine administration, events outcome, the evaluation did not find evidence to exclude a reasonable possibility of a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD: Preterm delivery with exposure of one dose of COVID-19 VACCINE ASTRAZENECA during pregnancy at an unknown gestational age. The preterm baby was delivered at PPD. The PPD had PPD second dose one month later.

AstraZeneca Comment: Due to limited information on patient age, exact onset date of events reported, relevant medical and family history, circumstances leading to the events, weeks of pregnancy, risk factors PPD), other concomitant medications and vaccination history, detailed diagnostic and etiologic workup (complete blood panel with infectious profile, ultrasound scans, echocardiogram, oxygen saturation, neonatologist opinion, neurological workup of the neonate), clarification regarding route of vaccine administration, events outcome, the evaluation did not find evidence to exclude a reasonable possibility of a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD: This case is a report from a consumer concerning the neonate of a PPD-year-old PPD, with a medical history of PPD. Concomitant medications during pregnancy are PPD. The PPD received first dose of COVID-19 VACCINE ASTRAZENECA at PPD of gestational age (PPD), the second dose was given 2 months later. On PPD heart rate decreased and on PPD the

neonate was born prematurely. The neonate was found to have developed neonatal sepsis. The outcome of neonatal sepsis and premature birth is unknown.

AstraZeneca Comment: Due to limited information on relevant intrauterine medical history, risk factors (PPD), concomitant medications, detailed diagnostic and etiologic workup (complete physical exam, complete laboratory test, relevant imaging studies), the evaluation did not find evidence to exclude a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** Premature neonate with unknown time to exposure to COVID-19 VACCINE ASTRAZENECA during gestation. Neonatal PPD and prematurity were reported at an unknown gestational age. No additional information is available.

AstraZeneca Comment: Due to limited information on patient age, date of vaccination, onset date of events, relevant medical and family history, circumstances leading to the events, weeks of pregnancy, risk factors (PPD), other concomitant medications and vaccination history, detailed diagnostic and etiologic workup (complete blood panel with infectious profile, ultrasound scans, echocardiogram, oxygen saturation, neonatologist opinion, neurological workup of the neonate), events outcome, the evaluation did not find evidence to suggest a causal relationship between the events and vaccine COVID-19 VACCINE ASTRAZENECA.

PPD **:** Concerning a PPD patient of Unknown ethnic origin born in PPD (weight PPD kg). No information regarding the medical history was reported. Concomitant medication included PPD Reporter stated that PPD obstetrical history included PPD On PPD , at gestational age PPD , the PPD of the neonate received the first dose of *COVID-19 VACCINE ASTRAZENECA*. On PPD , at gestational age PPD , the PPD of the neonate received the second dose of *COVID-19 VACCINE ASTRAZENECA*. On an unknown date, the patient experienced PPD (preferred term: Premature baby), COVID-19 (preferred term: COVID-19), PPD . Neonate's birth weight was PPD , body length not reported. The neonate spent seven days in the hospital after birth and was in the PPD due to prematurity. The outcome of the

event(s) of birth at gestational age PPD, COVID-19 and PPD was unknown.

AstraZeneca Comment: Due to limited information on patient age, date of vaccination, onset date of events, relevant medical and family history, circumstances leading to the events, weeks of pregnancy, risk factors (PPD), other concomitant medications and vaccination history, detailed diagnostic and etiologic workup (complete blood panel with infectious profile, ultrasound scans, echocardiogram, oxygen saturation, neonatologist opinion, neurological workup of the neonate), events outcome, the evaluation did not find evidence to suggest a causal relationship between the events and vaccine COVID-19 VACCINE ASTRAZENECA.

Retardation of neonatal growth.

PPD: A report has been received from a consumer, regarding a subject enrolled in study D8110C00003, COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) concerning a PPD patient (age not provided) of Unknown ethnic origin (weight PPD kg). No medical history was reported and no concomitant products were reported. On PPD, the patient received the first dose of *COVID-19 VACCINE ASTRAZENECA*. On PPD, the patient received the second dose of *COVID-19 VACCINE ASTRAZENECA*. On PPD, the patient experienced PPD medical history included PPD The outcome of the events of PPD was unknown.

AstraZeneca Comment: Due to limited information on concurrent diseases, detailed obstetric history, possible risk factors(PPD), and detailed diagnostic and etiologic workup (physical examination, blood laboratory tests, infection profile, imaging studies, neonatology assessment), the evaluation did not find evidence to exclude reasonable possibility of a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

Stillbirth

PPD**:** Spontaneous report from a consumer concerning a stillbirth as an outcome of a pregnancy from a PPD-year-old PPD. It was reported that the PPD had medical history of PPD (dates not reported). It was reported that the patient did not know PPD had high blood pressure or

PPD . The patient received COVID-19 VACCINE ASTRAZENECA on PPD and the patient experience stillbirth the same day.

AstraZeneca Comment: Due to limited information on circumstances leading to the events, patient baseline health characteristics before vaccination, exact date of vaccination, pregnancy course details and complete clinical course of the events, date of death, autopsy report details, other detailed medical history, concomitant medications, family history, risk factors and comorbidities (PPD), detailed diagnostic and etiologic workup (serum electrolyte levels, biochemical blood analysis, complete blood panel with white blood cell differential test, erythrocyte sedimentation rate, Covid-19 polymerase chain reaction test results, other viral and bacterial infection panel, immune profile, beta-human chorionic gonadotropin level, gynaecology examination, Holter blood pressure monitoring, ultrasonography, electrocardiogram), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** Spontaneous report from PPD , via a healthcare professional, concerning a stillbirth case as an outcome of a PPD year-old PPD . Concomitant medications included PPD The PPD received dose one of COVID-19 VACCINE ASTRAZENECA on PPD and second dose on the PPD . On an unknown date the PPD patient experienced PPD and stillbirth on PPD . It was reported that the patient was PPD . Neonatal case of stillbirth is PPD . Autopsy was performed according to the narrative, but results are not yet available.

AstraZeneca Comment: Due to limited information on baseline health conditions before vaccination, circumstances leading to the events, onset dates for the events, relevant medical history (PPD), concurrent conditions (PPD), risk factors PPD) and autopsy report, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** PPD -year-old-PPD vaccinee. The vaccinee received both doses PPD ; first dose at PPD and the second dose at PPD . At PPD gestation, the vaccinee had a stillbirth. Events of PPD were also reported

on unknown dates. It was reported the vaccinee did not know PPD had PPD until after the stillbirth. Post-mortem results concluded the baby had died due to the PPD ; nothing else structurally or congenital and normal placenta.

AstraZeneca Comment: Due to limited information on circumstances leading to the events, concurrent conditions, detailed etiological and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the fatal events and COVID-19 VACCINE ASTRAZENECA.

PPD : A neonate of unknown gender whose PPD -year-old PPD with a history of PPD received *COVID-19 VACCINE ASTRAZENECA* on PPD . On PPD , the Baby's heart progressively slowed and stopped after 5 weeks monitoring. The baby died (PT: Stillbirth) on PPD

AstraZeneca Comment: Due to limited information on baseline health condition before vaccination, relevant medical history, autopsy (if done), details and circumstances surrounding the events, risk factors (PPD , the evaluation did not find evidence to exclude a reasonable possibility of a causal relationship between fatal events and COVID-19 VACCINE ASTRAZENECA.

PPD **:** A spontaneous report has been received from the regulatory authority in PPD . Via healthcare professional, concerning a PPD -year-old PPD patient. The patient's past and current medical history included PPD Concomitant medication included PPD The patient received the first dose of *COVID-19 VACCINE ASTRAZENECA* on PPD . The patient received the second dose of *COVID-19 VACCINE ASTRAZENECA* on PPD . On an unknown date, the patient experienced PPD Nine days after the second dose of *COVID-19 VACCINE ASTRAZENECA* the patient had a still birth at approximately PPD . Patient did not take PPD

AstraZeneca Comment: Due to limited information on relevant medical and family history, circumstances leading to the event, other risk factors (PPD), concomitant medications and vaccination history, detailed diagnostic and etiologic workup (blood tests, urinalysis, fetal ultrasound, nonstress test,

biophysical profile), the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between events and suspect drug.

PPD **:** A spontaneous report had been received from the regulatory authority in PPD via health professional. PPD -year-old PPD with medical history of PPD The patient received first dose of *COVID-19 VACCINE ASTRAZENECA* via transplacental route on PPD and a second dose of *COVID-19 VACCINE ASTRAZENECA* via transplacental route on PPD. The PPD did not take PPD during pregnancy. The patient died (MedDRA PT: Stillbirth) on PPD. The cause of death was stillbirth. Autopsy was performed however no results are available.

AstraZeneca Comment: Due to limited information on baseline health condition before vaccination, relevant medical history, concomitant medications, details and circumstances surrounding the event, clinical course and details of the treatment provided, possible risk factor (PPD), complete details of mothers medical conditions and detailed diagnostic and etiologic workup (gynaecological workup, complete blood analysis), the evaluation did not find evidence to suggest a causal relationship between the event and COVID-19 VACCINE ASTRAZENECA.

Conclusion
From the data identified cumulatively and during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between these events reported in neonates and COVID-19 VACCINE ASTRAZENECA. Pregnancy and neonatal outcomes continue to be kept under close surveillance by AstraZeneca.

16.3.4 New information on other identified risks not categorised as important

Reactogenicity was considered as a relevant topic for COVID-19 VACCINE ASTRAZENECA and has not been presented elsewhere in this PSUR. An updated cumulative review of this topic is provided in Section 16.3.4.1.

16.3.4.1 Reactogenicity

A cumulative search of the AstraZeneca global safety database through 28 December 2021 was conducted to identify serious, medically confirmed cases of reactogenicity with COVID-19 ASTRAZENECA VACCINE. The PTs used to define reactogenicity included: Headache, Nausea, Vomiting, Myalgia/muscle pain, Arthralgia/joint pain, Injection site bruising, Injection site pain, Injection site pruritus, Injection site swelling, Injection site warmth, Injection site erythema, Fatigue, Malaise, Chills, Fever /Pyrexia and Lymphadenopathy.

For the reporting period, a total of 181669 cases involving 504004 events of reactogenicity were identified from the global safety database. Of these 181669 cases, there were 4595

serious, medically confirmed cases of reactogenic events with COVID-19 ASTRAZENECA VACCINE. Of the 4595 cases, 2995 (65%) occurred in females, 1558 (34%) in males, and 42 (1%) of unknown gender. Of these 4595 cases, the distribution of the reactogenic events were as follows: Headache (2055), Pyrexia (1957), Myalgia (904), Fatigue (878), Nausea (652), Malaise (581), Chills (574), Arthralgia (548), Vomiting (531), Injection site pain (116), Lymphadenopathy (94), Injection site erythema (26), Injection site swelling (21), Injection site warmth (12), Injection site pruritus (4) and Injection site bruising (2).

Cumulatively, a total of 435038 cases involving 1214627 adverse events of reactogenicity were identified from the global safety database. Of these 435038 cases, there were 12216 serious, medically confirmed cases of reactogenic events with COVID-19 ASTRAZENECA VACCINE . Of the 12216 cases, 8624 (70%) occurred in females, 3396 (28%) in males, and 196 (2%) cases were of unknown gender. Of these 12216 cases, the distribution of the reactogenic events were as follows: Headache (5813 events), Pyrexia (5754 events), Myalgia (2483 events), Fatigue (2427events), Nausea (2245 events), Chills (2139 events), Malaise (1633 events), Arthralgia (1613 events), Vomiting (1567 events), Injection site pain (379 events), Injection site erythema (67events), Injection site swelling (45 events), Injection site warmth (23 events), Injection site pruritus (11 events), and Injection site bruising (3 events).

Reactogenicity is considered appropriately described in the COVID-19 VACCINE ASTRAZENECA CDS. A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

16.3.5 Update on missing information

All concepts considered as missing information for the Core RMP are provided in Section 16.1 and in Table 149 below.

Table 149 Missing information presented in Core RMP (Version 3.0; dated 28 April 2021)

Section/Topic	Core RMP
Important potential risk	Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women Use of COVID-19 VACCINE ASTRAZENCA in subjects with severe immunodeficiency Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease Use of COVID-19 VACCINE ASTRAZENECA with other vaccines

RMP Risk Management Plan.

16.3.5.1 Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding

16.3.5.1.1 Use of COVID-19 VACCINE in Pregnant Women

Review of Cases

Reports of pregnancy were retrieved from the AstraZeneca global safety database using the key ingredient AZD1222 and the AstraZeneca customized 'PSUR pregnancy' business objects report which includes the following search criteria:

The field Pregnant is marked as YES or Events code to one of the Medical Dictionary for Regulatory Activities (MedDRA) (Version 24.1) System Organ Classes (SOCs): Congenital, familial and genetic disorders, Pregnancy, puerperium and perinatal conditions or Events code to the MedDRA High-level Group Term: Foetal and neonatal investigations or Events code to one of the MedDRA High-level Terms: Induced abortion complications, Induced abortions or Events code to one of the MedDRA Preferred Terms (PTs): Aborted pregnancy, Amastia, Amnioscopy, Amnioscopy abnormal, Amnioscopy normal, Ectopic pregnancy termination, External cephalic version, Pregnancy of partner, Pregnancy test positive, Pregnancy test urine positive, Hyperplasia adrenal and Macroorchidism. Cases describing Pregnancy with adverse neonatal outcomes are described in Section 16.3.3.1.

Interval Review (29 June 2021 – 28 December 2021)

During the reporting period, 2614 case reports were retrieved using the above search strategy; however, 323 case reports were excluded for the following reasons:

- There were 251 reports that were without pregnancies/breastfeeding (review of these cases did not support pregnancy).
- In 13 reports, there was a coding error and review of these cases did not support pregnancy.
- There were 59 reports that were non-valid (duplicate cases or invalid cases without AE reports).

The remaining 2291 cases were considered for further analysis. Of the 2291 reports, 1936 reports included pregnancy/breastfeeding reports with other AEs and 355 reports were without AEs.

Of the 2291 reports of exposure to AZD1222 during or before pregnancy/breastfeeding, 18 were from interventional clinical trials, 488 were from post-marketing studies, and 1785 were spontaneous. Of these 2291 reports, 356 were medically confirmed (117 serious and 239 non serious).

Outcome of pregnancy cases (excluding cases of breastfeeding) are summarized below:

Of the total 2291 case reports, there were 1885 reports with unknown or N/A pregnancy outcome. A total of 403 cases reported an outcome; one case (PPD) included a PPD combination and the outcome is counted only once. PPD was a PPD case to PPD was PPD case to PPD .

Of the 403 case reports with an outcome, there were 300 cases of spontaneous abortion (2 with foetal malformation, 8 abortion missed), 33 case reports with congenital anomaly, 39 case reports of healthy baby without congenital anomaly or AE, 10 case reports of elective abortion (3 with congenital anomalies), 8 case reports of stillbirth, 12 case reports of premature babies, 2 case reports of foetal death, 1 case report with breech presentation, and 1 case report of ectopic pregnancy (some of these reports fell into more than 1 category, so the total may not add up to 403).

Spontaneous Abortion – Interval Review

A total of 300 pregnancy cases resulted in spontaneous abortion, of which 83% (250 out of 300) were reports from consumers and 17% of the reports were medically confirmed, with 65% of the reports being from the UK. Age was reported in 259 of the 300 case reports; median age was 34 years (range: from 19 to 46 years; 27 reports in women aged < 25 years and 131 reports in women aged 26 to 35 years and 101 reports were in women aged > 36 years). In 153 of the 300 reports, gestational week at the time spontaneous abortion was unknown; in the remaining 147 reports, 131 (89%) occurred in the 1st trimester, 13 (9%) were during the 2nd trimester, and 3 (2%) were during the 3rd trimester.

Adverse Maternal Outcomes – Interval Review

Maternal outcomes that are part of the AE of special interest concept of "Pregnancy outcome – maternal" (as presented in the risk management plan) are shown in Table 150.

Table 150 Adverse Maternal Outcomes

PT	Event count
Gestational diabetes	10
Pre-eclampsia	10
Caesarean section	4
Placenta praevia	4
Eclampsia	3
Premature labour	3
Grand Total	**34**

PT, preferred term.

Of the 34 cases with adverse maternal outcomes, 10 cases reported risk factors for the adverse maternal outcomes.

The number of adverse maternal outcomes is small in relation to the exposure. No safety concern is identified.

Abnormal Neonatal Outcomes – Interval Review

There were 47 cases with abnormal neonatal outcomes.

Cases included Congenital anomalies (25), Abortion missed (5), foetal death (2), Breech presentation (1), anencephaly incompatible with life (1), Foetal malformation/Gastroschisis/Hypoplastic right heart syndrome (1), Foetal malformation/Mitral valve atresia (1), Spontaneous abortion/Foetal malformation (2), foetal distress syndrome (1), foetal growth restriction (2).

The 2 foetal death cases (PPD) are summarised in the cumulative review below.

Information available in most of the cases was limited.

The number of abnormal neonatal outcomes is small in relation to the exposure. No safety concern is identified.

Fatal Cases, Excluding Pregnancy and Neonatal Outcomes – Interval Review

Of the 2291 case reports, there were 5 reports of fatal outcome not related to pregnancy and neonatal outcomes occurring in Mexico (2), Brazil (2), and India (1).

Two cases were related to thrombosis in combination with thrombocytopenia (1 from PPD and 1 from PPD). Both cases are summarised in the thrombosis in combination with thrombocytopenia section of this report (below).

See summaries below for cases PPD .

Adverse Events Reported in the Pregnancy Cases - Interval Review

Of the 2291 pregnancy cases, 1936 cases had reported AEs. Most of the AEs reported in these cases were known reactogenicity events (Headache, Pyrexia, Fatigue, Chills, Myalgia, Nausea, Pain in extremity and Arthralgia). There was no trend or signal seen from these AEs reported from the pregnancy cases.

Thrombosis in Combination with Thrombocytopenia Pregnancy – Interval Review

For context in relation to the background risk in pregnancy of Thrombosis with Thrombocytopenia Syndrome, in the pregnancy guidance from the Royal College of Obstetricians and Gynaecologists relating to COVID-19 infection (RCOG 2021), it is noted that although pregnancy increases the risk of coagulopathy, there is no evidence that pregnant or postpartum women are at higher risk of Thrombosis with Thrombocytopenia Syndrome (TTS) than non-pregnant women.

Three (3) cases of thrombosis in combination with thrombocytopenia in pregnancy were reported from 2291 pregnancy reports (1 each from [redacted] during the reporting period.

All events were reported after Dose 1 and TTO was within 21 days in 2 of 3 cases (2, 10 days, and unknown). Outcome was fatal in 2 reports and unknown in the other report.

One (1) fatal case from [redacted] met the possible criteria for TTS based on MHRA classification.

Neither of the cases from PPD met the criteria for TTS based on MHRA case classification.

Case summary narratives are presented below.

Review of Cases – Cumulative through 28 December 2021

Cumulatively through 28 December 2021, 4524 case reports were retrieved using the above search; however, 605 case reports were excluded for the following reasons:

- There were 487 reports that were without pregnancies/breastfeeding (review of these cases did not support pregnancy).
- In 17 reports, there was a coding error and review of these cases did not support pregnancy.
- There were 101 reports that were non-valid (duplicate cases or invalid cases without AE reports).

The remaining 3919 cases were considered for further analysis. Of the 3919 reports, 3509 reports included pregnancy/breastfeeding reports with other AEs and 410 reports were without AEs.

Of the 3919 reports of exposure to AZD1222 during or before pregnancy/breastfeeding, 19 were from interventional clinical trials, 488 were from post-marketing studies, and 3412 were spontaneous. Of these 3919 reports, 536 were medically confirmed (184 serious and 352 non serious).

Outcome of pregnancy cases (excluding cases of breastfeeding) are summarized below:

Of the total 3919 case reports, there were 3443 reports with unknown or N/A pregnancy outcome. A total of 473 cases reported an outcome; one case (PPD) included a PPD combination and the outcome is counted only once. PPD was a PPD case to PPD was PPD case to PPD

Of the 473 case reports with an outcome, there were 368 cases of spontaneous abortion (3 with foetal malformation, 8 abortion missed), 33 case reports with congenital anomaly, 42 case reports of healthy baby without congenital anomaly or AE, 11 case reports of elective abortion (3 with congenital anomalies), 9 case reports of stillbirth, 12 case reports of premature babies, 2 case reports of foetal death, 1 case report with breech presentation, and 1 case report of ectopic pregnancy, (some of these reports fell into more than 1 category, so the total may not add up to 473).

Spontaneous Abortion – Cumulative Review

A total of 368 pregnancy cases resulted in spontaneous abortion. A total of 81% (299 out of 368) were reports from consumers and 19% of the reports were medically confirmed, with 67% of the reports being from the UK. Age was reported in 317 of the 368 case reports; median age was 34 years (range: from 19 to 46 years; 30 reports in women aged < 25 years and 158 reports in women aged 26 to 35 years and 130 reports were in women aged > 36 years). In 186 of the 368 reports, gestational week at the time spontaneous abortion was unknown; in the remaining 182 reports, 163 (90%) occurred in the 1st trimester, 16 (8%) were during the 2nd trimester, and 3 (2%) were during the 3rd trimester.

Observed Vs. Expected Analysis – Spontaneous abortion

The incidence rates for spontaneous abortions were calculated based on the reported rates by Hemminki and Forssas 1999 data on conceptions among women in England and Wales, 2018 from the UK Office of National Statistics (Conceptions in England and Wales 2018) to estimate the rates of spontaneous abortions per 100,000 women years.

Vaccine administration data based on the age and gender is only available from UK and the below analysis was based on case reports from UK. The observed versus expected analysis of spontaneous abortions with DLP 28 December 2021 showed that observed cases occurred significantly less frequently than expected for overall and by different age stratifications from UK. A summary of spontaneous abortion observed versus expected analysis is presented in Table 151.

Table 151 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
18 to 24	1780.8	60	661657	3	1935.61	0 (0 - 0.1)	Observed significantly < expected
25 to 29	1437.5	60	677677	19	1600.3	0.01 (0.01 - 0.02)	Observed significantly < expected
30 to 34	1447	60	945726	34	2248.04	0.02 (0.01 - 0.02)	Observed significantly < expected
35 to 39	864.6	60	1150622	46	1634.25	0.03 (0.02 - 0.04)	Observed significantly < expected
40 to 44	223.3	60	2382386	23	873.92	0.03 (0.02 - 0.04)	Observed significantly < expected
18 to 24 plus Unk TTO	1780.8	60	661657	9	1935.61	0 (0 - 0.01)	Observed significantly < expected
25 to 29plus Unk TTO	1437.5	60	677677	25	1600.3	0.02 (0.01 - 0.02)	Observed significantly < expected
30 to 34 plus Unk TTO	1447	60	945726	54	2248.04	0.02 (0.02 - 0.03)	Observed significantly < expected
35 to 39 60 plus Unk TTO	864.6	60	1150622	71	1634.25	0.04 (0.03 - 0.05)	Observed significantly < expected
40 to 44 60 plus Unk TTO	223.3	60	2382386	32	873.92	0.04 (0.03 - 0.05)	Observed significantly < expected
All ages	995.3	60	8410118	142	13750.74	0.01 (0.01 - 0.01)	Observed significantly < expected
All ages plus Unk TTO	995.3	60	8410118	238	13750.74	0.02 (0.02 - 0.02)	Observed significantly < expected

IR, Incidence Rate; PY, Person Years; TTO Time to onset; UK, United Kingdom; Unk Unknown.

Adverse Maternal outcomes – Cumulative Review

Maternal outcomes that are part of the AE of special interest concept of "Pregnancy outcome – maternal" (as presented in the risk management plan) are shown in Table 152.

Table 152 Adverse Maternal Outcomes – Cumulative period

PT	Event count
Gestational diabetes	15
Pre-eclampsia	11
Premature labour	6
Caesarean section	4
Placenta praevia	4
Eclampsia	3
Uterine rupture	1
Grand Total	**44**

PT, Preferred Term.

Of the 44 cases with adverse maternal outcomes, 17 cases reported risk factors for the adverse maternal outcomes. For example, 6 cases of gestational diabetes reported previous history of gestational diabetes.

The number of adverse maternal outcomes is small in relation to the exposure. No safety concern is identified.

Abnormal Neonatal Outcomes – Cumulative Review

There were 48 cases with abnormal neonatal outcomes.

Cases included Congenital anomalies (27), Abortion missed (8), foetal death (2), Breech presentation (1), anencephaly incompatible with life (1), Foetal malformation/Gastroschisis/Hypoplastic right heart syndrome (1), Foetal malformation/Mitral valve atresia (1), Spontaneous abortion/Foetal malformation (3), foetal distress syndrome (1), foetal growth restriction (3).

The 2 foetal death cases are summarised below.

- PPD : A spontaneous report of a PPD born in PPD (age PPD) who received the vaccine on PPD during unknown PPD . It was reported the foetus died (PT: Foetal Death) on an unspecified date. The cause of death was foetal death. No further information was available.
- PPD : A spontaneous report of a foetus of unknown gender who received the vaccine on an unknown date. The foetus died (PT: Foetal Death) on an

unspecified date. It was not known whether an autopsy was performed. It was reported PPD cause of death was PPD no longer developed. No further information was available.

Information available in most of the cases was limited.

The number of abnormal neonatal outcomes is small in relation to the exposure. No safety concern is identified.

Fatal Cases, Excluding Pregnancy and Neonatal Outcomes – Cumulative Review

Of the 3919 case reports, there were 10 reports of fatal outcome not related to pregnancy and neonatal outcomes.

Seven (7) of the case reports were from Brazil (1 reported by a consumer in the [redacted] concerning a vaccinee in Brazil), 2 from Mexico, and 1 from [redacted].

Four (4) case reports (3 cases from PPD) and 1 case reported from a consumer in the PPD related to a thrombosis in combination with thrombocytopenia case in PPD) are potential duplicates of PPD . The remaining 6 unique cases are discussed below:

Three cases were related to thrombosis in combination with thrombocytopenia (2 from PPD [PPD] and 1 from PPD). These cases are summarised in the later thrombosis in combination with thrombocytopenia section of this report.

- PPD year old PPD (consumer report), received AZD1222 vaccine at PPD and died 3 days later due to Respiratory insufficiency.
- PPD year old PPD (consumer report), at PPD received AZD1222. The next day PPD experienced Headache and Pyrexia. Four days later PPD experienced Thrombocytopenia; Seizure; Myalgia; Arthralgia; Pruritus; Purpura; Nausea; Cerebral haematoma; Petechiae; Oedema peripheral; PPD died on an unspecified date. No further information was available.
- PPD (a health professional report) born in PPD (age PPD), received the first dose of AZD1222 vaccine on PPD and the second dose of COVID-19-mRNA, Pfizer vaccine on PPD during unknown PPD On PPD experienced PPD and PPD The outcome of the event of PPD was unknown. The patient died from the event of

PPD on an unspecified date. It was not known whether an autopsy was performed. The cause of death was abdominal pain and maternal exposure during pregnancy.

Adverse Events Reported in the Pregnancy Cases – Cumulative Review

Of the 3919 cases, 3509 cases had reported AEs. Most of the AEs reported in these cases were known reactogenicity events (Headache, Pyrexia, Fatigue, Chills, Myalgia, Nausea, Pain in extremity and Arthralgia). There was no trend or signal seen from these AEs reported from the pregnancy cases.

Thrombosis in Combination with Thrombocytopenia Pregnancy Case Summary – Cumulative Review

Five (5) cases of thrombosis in combination with thrombocytopenia in pregnancy were reported from 3919 pregnancy reports (2 from Brazil and 1 each from [redacted] and [redacted] .

All events were reported after Dose 1 and TTO was within 21 days in 4 of 5 cases (2, 10, 14, 15 days, and unknown). Outcome was fatal in 3 reports, not recovered in 1, and in the other report outcome was unknown.

One (1) fatal case from [redacted] and one (1) from [redacted] met the confirmed and possible criteria for TTS based on MHRA classification respectively.

Neither of the cases from [redacted] and one (1) case from [redacted] met the criteria for TTS based on MHRA case classification.

Case summary narratives are presented below.

- PPD : PPD -year-old from the PPD (medically confirmed report), medical history included PPD Received Dose 1 of COVID-19 VACCINE ASTRAZENECA on PPD confirmed PPD , and experienced COVID-19 infection on PPD developed Pulmonary embolism and deep vein thrombosis on PPD 1, platelet counts were normal 180 (reference range 150-450). Outcome was not recovered. Outcome of pregnancy was unknown. No further information was available.

  AstraZeneca Comment: Due to limited information on circumstances leading to the events, details on pregnancy, other concurrent conditions as infection, concomitant medications (hormones), relevant medical history including PPD

PPD , family history, detailed etiological and diagnostic workup (complete blood analysis, infectious disease tests, clinical assessment, coagulation panel, anti-platelet factor 4 antibodies, imaging studies as venous doppler or other relevant studies), the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : A spontaneous report from a consumer via the Regulatory Authority in Mexico concerning a PPD-year old PPD . No medical history and concomitant medication were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD and was PPD Two days later PPD experienced thrombotic thrombocytopenic purpura, PPD , sensitivity (preferred term: Tenderness), reduced muscle strength, petechias on feet ankle, respiratory distress, dyspnoea, nocturnal dyspnoea, lumbar pain, injection site pain, knee pain, fever greater than or equal to 38 degrees Celsius, headache, fatigue, asthenia, chills, and myalgia. Outcome of events and outcome of pregnancy was unknown. No further information was available.

  AstraZeneca Comment: Due to limited information on baseline health condition before vaccination, family and medical history, concurrent conditions (PPD , risk factors (PPD), etiological and diagnostic work up (haematologist, obstetrician and neurologist assessment, complete blood analysis with coagulation panel and infectious profile, blood pressure readings, relevant imaging studies, echocardiogram, electrocardiogram), clinical course and treatment details, the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : A PPD of unknown age from PPD (literature report) received COVID-19 VACCINE ASTRAZENECA on an unknown date. The reported term was "PPD experienced thrombocytopenia syndrome (TTS) that resulted in maternal and foetal death after receiving the COVID-19 vaccine (AstraZeneca vaccine)" on an unknown date. The PPD died due to thrombocytopenia thrombosis syndrome (TTS) on an unspecified date. It is not known whether an autopsy was performed.

  AstraZeneca Comment: Due to limited information on predisposing risk factors PPD , event onset date and vaccine receipt date, relevant medical history, concurrent conditions, concomitant medications, diagnostic and etiologic workup, autopsy details; the evaluation did not

find the evidence to suggest a causal relationship between the fatal event and COVID-19 VACCINE ASTRAZENECA.

- PPD : A PPD -year-old PPD from PPD , with medical history including controlled hypothyroidism had 2 episodes of urinary tract infection received COVID-19 VACCINE ASTRAZENECA on PPD . On PPD , emergency due to headache, nausea, and pain in legs and hip, blood count with 121000/mm^3 platelets, and urine culture-negative (verbal information). On PPD , the patient sought the emergency with headache and instantly after the computed tomography (CT) scan of the PPD Medical diagnosis suggestive of probably haemorrhagic stroke associated with sinus venous thrombosis. The patient underwent PPD on PPD . at 21:00 on PPD . On PPD , foetal death was found. Patient hospitalized in the PPD Clinical suspicion was TTS. Death occurred on PPD . Histopathological result of the placenta identified PPD

  AZ Comment: Due to limited information on risk factors (PPD , circumstances surrounding the events, other concurrent conditions, concomitant medications, relevant medical history, detailed etiological and diagnostic work-up (complete blood analysis, electroencephalogram, magnetic resonance imaging, physical examination, pre-vaccination platelet count) the evaluation did not find evidence to suggest a causal relationship between the events and COVID-19 VACCINE ASTRAZENECA.

- PPD : PPD -year-old PPD (consumer report) from PPD , born as PPD experienced PPD , cerebral venous thrombosis, and vaccine-associated thrombocytopenia, after receiving COVID-19 VACCINE ASTRAZENECA during pregnancy. The consumer was immunized with first dose of COVID-19 VACCINE ASTRAZENECA vaccine on PPD . On PPD , patient experienced a mild headache and upper abdominal pain which became severe PPD PPD After no change in pain, PPD on PPD . Nine days after vaccination, on PPD developed a severe headache and was PPD , patient became unconscious and unresponsive.. Patient was in a critical

stage with low "CGS" and anisocoria, PPD condition was serious during that time, and PPD was put on ventilator. MRI scan suggestive of PPD On PPD, hospital declared PPD, patient was ventilated for 6 days and died on PPD. In the death report, Post mortem certificate suggested the cause of death to be PPD and the hospital stated cerebral venous thrombosis and vaccine-associated thrombocytopenia as the causes of death. PPD pregnancy ultrasound scan on PPD additionally showed: CRL was 9.90 mm, corresponding to PPD, FHR was 150 bpm, uterine fibroid and expected delivery date was PPD

AZ Comment: Due to limited information on circumstances leading to the events, details on concurrent condition, family history, concomitant medications, clinical course, baseline health characteristics of the vaccinee before vaccination, risk factors (PPD), details of treatment provided, complete etiological and diagnostic workup (complete blood analysis, physical examination, coagulation profile, autopsy details), the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Literature Review - Pregnancy

- Rathberger et al 2021 investigated the effects of COVID-19 infection in pregnancy especially regarding a possible fetal transmission of antibodies to SARS-CoV-2 and the longevity of this immunity. Sixteen women who were infected with SARS-CoV-2 during pregnancy and their offspring were included. The antibody response to SARS-CoV-2 was measured in mother and umbilical cord blood peripartum and in a follow-up examination 6-11 weeks after birth. A total of 73% of the women and one third of the infants developed antibodies to SARS-CoV-2 spike (S) protein receptor binding domain, with a long interval between infection and birth proving favorable for a transplacental transfer of antibodies to the neonates. All infants showed declining or vanishing antibody-titers in the follow-up examination, while the titers of their mothers were stable or even increased. The study showed that transplacental transfer of SARS-CoV-2-specific antibodies is possible, but also indicate that the immunity that may be gained as a result might decrease in newborns postpartum. In addition to transplacental transfer of specific antibodies the authors noted a robust transfer via breastmilk in those mothers with high titers at birth and supports the recommendations to continue breastfeeding during mild-to-moderate maternal COVID-19 disease.

  AstraZeneca Comment: This study did not involve the use of vaccines. Although sample size is small, the study demonstrated fetal transmission of antibodies to SARS-

CoV-2 from women infected during pregnancy as well as transfer via breastmilk in those mothers with high titers at birth.

- Pham et al 2021 conducted a brief literature review on maternal COVID-19, vaccination safety in pregnancy, and evidence of protective immunity. The authors noted that early data from developmental and reproductive toxicity studies for both the Pfizer and Moderna vaccine did not demonstrate direct or indirect harmful effects with respect to pregnancy, fetal development, delivery, or postnatal complications. In addition, developmental and reproductive toxicity data on the Johnson & Johnson vaccine have not demonstrated adverse outcomes. Since the Emergency Use Authorization for the Pfizer and Moderna vaccines, more than 128,306 pregnant patients have received the vaccine and registered with the CDC V-safe program. Recent data from the CDC V-safe program found that side effects from the vaccine were similar between pregnant and nonpregnant women. In addition, when evaluating 827 completed pregnancies, there was no increased risk in adverse pregnancy outcomes including miscarriage, preterm birth, small for gestational age, and neonatal death when compared with data before the COVID-19 pandemic. The study found a robust maternal-induced humoral response to the vaccine that effectively transfers to the fetus, also supporting the role of vaccination during pregnancy.

  AstraZeneca Comment: The review focussed on mRNA COVID-19 vaccines, noting that pregnant individuals have a similar response to the vaccine as nonpregnant individuals and the benefits of these vaccines may outweigh the risks of COVID-19 in pregnancy and in the postpartum period.

- Ciaponi et al 2021 conducted a systematic review, to evaluate the safety of COVID-19 vaccines selected by the COVID-19 Vaccines Global Access-Maternal Immunization Working Group in August 2020, including their components and their technological platforms used in other vaccines for pregnant persons. They searched literature databases, COVID-19 vaccine pregnancy registries, and explored reference lists from the inception date to February 2021 without language restriction. 38 clinical and non-clinical studies (involving 2,398,855 pregnant persons and 56 pregnant animals) were included. Most studies (89%) were conducted in high-income countries and were cohort studies (57%). Most studies (76%) compared vaccine exposures with no exposure during the three trimesters of pregnancy. The most frequent exposure was to AS03 adjuvant, in the context of A/H1N1 pandemic influenza vaccines, (n = 24) and aluminum-based adjuvants (n = 11). Only one study reported exposure to messenger RNA in lipid nanoparticles COVID-19 vaccines. All studies concluded that there were no safety concerns. The authors found no evidence of pregnancy-associated safety concerns of COVID-19 vaccines or of their components or platforms when used in other vaccines, noting that the need for further data on several vaccine platforms and components, given their novelty. The authors concluded that it is reasonable to consider COVID-19 vaccination in pregnant women, because of their higher risk of adverse outcomes.

AstraZeneca Comment: The review found no evidence of pregnancy-associated safety concerns of COVID-19 vaccines or of their components or platforms when used in other vaccines.

- Theiler et al 2021 investigated pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. The authors combined a comprehensive vaccine registry with a delivery database for an integrated healthcare system to create a delivery cohort including vaccinated patients. Among the vaccinated patients, 1 received the Janssen COVID-19 vaccine, 12 received the Moderna vaccine, and 127 received the Pfizer-BioNTech vaccine. The median gestational age at first vaccination was 32 weeks (range 13 6/7-40 4/7), and patients vaccinated during pregnancy were less likely than unvaccinated patients to experience COVID-19 infection prior to delivery (1.4% (2/140) vs. 11.3% (210/1862), P<0.001). No maternal COVID-19 infections occurred after vaccination during pregnancy. No significant difference in the composite adverse outcome (5.0% (7/140) vs. 4.9% (91/1862), P=0.95) or other maternal or neonatal complications, including thromboembolic events and preterm birth, was observed in vaccinated compared to unvaccinated patients. The authors concluded that vaccinated pregnant women in this birth cohort were less likely to experience COVID-19 infection compared to unvaccinated pregnant patients, and COVID-19 vaccination during pregnancy was not associated with increased pregnancy or delivery complications.

  AstraZeneca Comment: This study found that COVID-19 vaccination during pregnancy is protective against maternal SARS-CoV-2 infection and that no pattern of adverse maternal or birth outcomes was evident after vaccination during pregnancy.

- Joubert et al 2021 provided an updated literature review on COVID-19 and novel mRNA vaccines in pregnancy. The authors reported current information and evidence available to aid in the decision whether to vaccinate against COVID-19 currently being made by pregnant individuals and their healthcare providers so that they are able to make a well-informed recommendation and decision. They highlighted a study of patients enrolled in the v-safe pregnancy registry who had at least one dose of an mRNA COVID-19 vaccine preconception or prior to 20 weeks' gestation and who did not report a pregnancy loss before six completed weeks' gestation to assess the cumulative risk of spontaneous abortion (SAB). Among 2456 pregnant persons who received an mRNA COVID-19 vaccine preconception or prior to 20 weeks' gestation, the cumulative risk of SAB from 6 to 19 weeks' gestation was 14.1%. When compared with the expected range of SABs in recognised pregnancies, these data suggest that receiving an mRNA COVID-19 vaccine preconception or during pregnancy is not associated with an increased risk of SAB. They noted that data collected in the V-safe registry (a voluntary smartphone-based surveillance system) so far include over 50 000 pregnant women with no serious vaccine-related adverse events; the UK has also created a similar registry for its citizens that shows similar results with no safety concerns related to COVID-19 vaccination; data from Pfizer/BioNTech, Moderna and

Janssen vaccines' animal DART studies have found no safety concerns with no adverse effect on female reproduction, fertility, fetal or embryonal, or postnatal development, miscarriage. The authors concluded that it will be essential to continue critically reviewing observational studies, clinical trials and available data for approval of vaccine use in pregnancy.

AstraZeneca Comment: The review found no safety concerns related to COVID-19 vaccination during pregnancy.

- Fahmy et al 2021 summarised the challenges to obstetric practice posed by the severe acute respiratory coronavirus 2 (COVID-19) pandemic. On vaccination the article highlighted the increasing evidence that COVID-19 vaccines are safe in pregnancy with the first dose to be administered ideally between 14 and 33 weeks of pregnancy. There is evidence of elevated SARS-CoV-2 Immunoglobulin G and A (IgG and IgA) antibodies in the breast milk of vaccinated mothers against the COVID-19 virus after one week of the initial dose which may offer protection for their babies. It was reported that 61.8% of tested breast milk samples turned positive for anti–SARS-CoV-2-specific IgA antibodies at 2 weeks post-first dose of vaccine and 86.1% positive at 1 week post-second dose. Anti–SARS-CoV-2-specific IgG antibodies meanwhile remained low during the first 3 weeks post vaccination but subsequently increased to 91.7% at week 4 and 97% at weeks 5 and 6. This is beneficial for breastfeeding mothers as these antibodies may provide some COVID-19 protection to their baby. However, further research must be conducted to verify the benefits of vaccination for this group of women.

  AstraZeneca Comment: The review highlighted the increasing evidence that COVID-19 vaccines are safe in pregnancy.

- Hillson et al 2021 presented the analysis of pregnancies in women of childbearing age participating in four phase 1, 2 and 3 ChAdOx1 nCoV-19 (AZD1222) vaccine clinical trials ongoing in 3 countries (UK, Brazil, South Africa). Out of 9755 participants, 121 (1%) reported pregnancy during the trial. Analysis of fertility outcome in 93 pregnant women (50 received ChAdOx1 and 43 received the control vaccine) showed no evidence of an association between reduced fertility and ChAdOx1 vaccination. The pregnancy outcome analysis in 107 women showed that risk of miscarriages was not higher in the ChAdOx1 group (72 women) than in the control group (35 women).

  AstraZeneca Comment: In this study, fertility was unaffected by vaccination with ChAdOx1 nCoV-19. Compared with women who received the control vaccine, there was no increased risk of miscarriage and no instances of stillbirth in women vaccinated before pregnancy in global clinical trials of ChAdOx1 nCoV-19.

- Leik et al 2021 reviewed COVID-19 vaccine and its consequences in pregnancy. The review summarised the rate of COVID-19 infection, maternal antibodies responsiveness, placenta antibody transmission, and adverse events after COVID-19 vaccination in pregnancy studied in epidemiological studies evaluating mRNA vaccines. The authors noted that potential COVID-19 infection in pregnant women can be prevented using mRNA-based vaccinations. Gestation, childbirth, and perinatal mortality were proven unaffected by COVID-19 vaccination. Injection-site discomfort, tiredness, and migraine are the most prevalent side effects, but these are temporary. After the first dosage of vaccinations, fast antibody responses were demonstrated. The adaptive immunity is found to be more significant after booster vaccination and is linked to improved placental antigen transmission. Two vaccination doses are associated with more robust maternal and fetal antibody levels. Longer delays between the first immunization dosage and birth are linked to greater fetal IgG antibody levels with reduction in antigen transmission proportion.

  AZ Comment: The review noted that mRNA vaccines are effective in reducing the severity of COVID-19 infection and these vaccinations are regarded to be safe options for pregnant women and their unborn foetus.

There is no evidence of safety concerns relating to use of COVID-19 vaccines in pregnancy in the literature articles presented.

Summary

In summary, the cumulative and periodic review up until 28 December 2021 of all reports of exposure to COVID-19 VACCINE ASTRAZENECA during pregnancy did not identify any safety concerns for the mother or the babies. The reported adverse events appear to be similar between the pregnant and non-pregnant populations.

The results of the O/E analyses for spontaneous abortion (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Based on the data from UK (including Scotland) and Norway, the risk of spontaneous abortion, stillbirth, premature delivery, low birthweight and perinatal mortality after COVID-19 AstraZeneca vaccination either before conception or during pregnancy is consistent with the expected risk in the unvaccinated pregnant women.

No specific risk factors, including pregnancy, have been identified for thrombosis in combination with thrombocytopenia.

Conclusion

During the late-breaking period, Section 4.7 (Pregnancy and Lactation) of the CDS for COVID-19 VACCINE ASTRAZENECA was updated to reflect current safety data regarding vaccine administration in pregnancy women, based on AstraZeneca global surveillance database, the pregnancy registry and literature. The recommendation was updated to consider the use of COVID-19 VACCINE ASTRAZENECA during pregnancy when the benefits outweigh the risks (see Section 14).

Based on these interval and cumulative reviews of the data, no updates to product labelling or RMP are needed. Use of COVID-19 VACCINE ASTRAZENECA during pregnancy remains as Missing information for the product.

16.3.5.1.2 Use of COVID-19 VACCINE ASTRAZENECA during Breastfeeding

Interval Period (29 June 2021 – 28 December 2021)

During the interval period, there were 487 reports pertaining to exposure to AZD1222 during lactation (478 for lactation and 9 for pregnancy/lactation exposure). Overall, 224 cases were serious (of which 5 were medically confirmed). Within these 487 reports, 93 cases (46 serious, 47 non-serious) reported 184 events in infants following breastfeeding. Of these 184 events, 93 were serious adverse events. Events occurring with a frequency of 5 or more in paediatric cases are shown in Table 153. No safety concern was identified.

Table 153 Adverse Events in Infants Following Breastfeeding (with a Frequency of ≥ 5 in Paediatric Cases)

Preferred Term	Non-serious	Serious	Total
Pyrexia	10	8	18
Irritability	3	9	12
Poor feeding infant	4	8	12
Crying	5	5	10
Diarrhoea	4	3	7
Vomiting	1	5	6
Infantile vomiting	3	3	6
Malaise	3	2	5
Somnolence	2	3	5
Infant irritability	3	2	5

There was one fatal case reported within the infant lactation cases (2021A567131), described in the cumulative review below.

In the interval review of reports of AZD1222 exposure during breastfeeding in the AstraZeneca Global Safety Database, there was limited information to suggest any reasonable

association between exposure to AZD1222 via breastfeeding and adverse outcomes in the neonates.

A total of 484 cases with AEs were reported in maternal vaccinees with 1805 events (1068 were serious and 737 were non-serious). A summary of the 10 most frequent AEs in maternal vaccinees is provided in Table 154. The most frequently reported AEs included headache, pyrexia chills, and fatigue. The AE profile was similar to the general population.

Table 154 Adverse Events in Maternal Vaccinees (Top 10 Frequencies)

Preferred Term	Non-serious	Serious	Total
Headache	39	51	90
Pyrexia	39	44	83
Chills	19	31	50
Fatigue	16	32	48
Heavy menstrual bleeding	18	27	45
Nausea	6	28	34
Pain	14	18	32
Arthralgia	7	19	26
Dizziness	8	17	25
Pain in extremity	11	13	24

There are no cases of thrombosis in combination with thrombocytopenia reported in the maternal vaccinees.

There were no maternal fatal cases relating to lactation.

Cumulative Review (29 December 2020 – 28 December 2021)

Cumulatively through 28 December 2021, there were 1771 reports pertaining to exposure to COVID-19 VACCINE ASTRAZENECA during lactation (1762 for lactation and 9 for pregnancy/lactation exposure). Overall, 1016 cases were serious (of which 22 were medically confirmed). Within these 1771 reports, 165 cases (74 serious, 91 non-serious) reported 322 events in infants following breastfeeding. Of these 322 events, 140 were serious adverse events. Events occurring with a frequency of 5 or more in paediatric cases are shown below. No safety concern was identified.

Table 155 Adverse Events in Infants Following Breastfeeding (with a Frequency of ≥ 5 in Paediatric Cases)

Preferred Term	Non-serious	Serious	Total
Pyrexia	23	15	**38**

Table 155 Adverse Events in Infants Following Breastfeeding (with a Frequency of ≥ 5 in Paediatric Cases)

Preferred Term	Non-serious	Serious	Total
Crying	14	8	**22**
Irritability	8	10	**18**
Poor feeding infant	7	11	**18**
Diarrhoea	9	4	**13**
Infant irritability	6	5	**11**
Somnolence	4	6	**10**
Malaise	5	4	**9**
Vomiting	4	5	**9**
Infantile vomiting	4	3	**7**
Restlessness	6	1	**7**
Chills	1	5	**6**
Rash	5	1	**6**
Pain	2	3	**5**
Fatigue	3	2	**5**
Lethargy	2	3	**5**

There was one fatal case reported within the infant lactation cases (PPD), described below.

- PPD **:** A spontaneous report from a consumer concerning a PPD old PPD infant from PPD whose PPD had been vaccinated on an unknown date. The infant died on PPD . It is not known whether an autopsy was performed. The reporter provided the following additional description: "The PPD said when PPD went to check on the PPD old infant at 3 a.m. PPD , four hours after PPD had foam and blood on PPD lips, and PPD was pronounced dead on arrival at hospital shortly after. The initial findings indicated that the PPD had died of PPD . The death of a PPD -old PPD was most likely was due to sudden infant death syndrome rather than from drinking mothers milk after the child's mother got vaccinated against COVID-19". No other information is available.

In the cumulative review of all reports of COVID-19 VACCINE ASTRAZENECA exposure during breastfeeding in the AstraZeneca Global Safety Database, there was limited information to suggest any reasonable association between exposure to COVID-19 VACCINE ASTRAZENECA via breastfeeding and adverse outcomes in the neonates.

A total of 1712 cases with AEs were reported in maternal vaccinees with 6082 events (4377 were serious and 1706 were non-serious). A summary of the 10 most frequent AEs in maternal vaccinees is provided in Table 156. The most frequently reported AEs included headache, pyrexia chills, and fatigue. The AE profile was similar to the general population.

Table 156 Adverse Events in Maternal Vaccinees (Top 10 Frequencies)

Preferred Term	Non-serious	Serious	Total
Headache	166	428	**594**
Pyrexia	136	375	**511**
Chills	92	301	**393**
Fatigue	76	255	**331**
Nausea	53	213	**266**
Myalgia	45	167	**212**
Dizziness	37	134	**171**
Pain	52	115	**167**
Pain in extremity	47	106	**153**
Arthralgia	35	113	**148**

Literature

- McLaurin-Jiang et al 2021 investigated whether vaccine-related side effects following COVID-19 vaccination were associated with an adverse impact on breastfeeding. Secondarily, the authors sought to determine perceived symptoms in breastfed children and maternal opinion about COVID-19 vaccination. The authors conducted a cross-sectional survey of breastfeeding mothers who underwent COVID-19 vaccination >2 days before the survey. Subjects were recruited through social media and websites. Data included sociodemographic information, vaccine history, maternal and child symptoms, and impact on lactation/breastfeeding. The analysis included 4,455 breastfeeding mothers. Maternal postvaccination symptoms were more common after the second dose ($p < 0.001$). The authors concluded that COVID-19 vaccination among breastfeeding mothers resulted in minimal disruption of lactation or adverse impact on the breastfed child, noting that the findings may be considered in vaccination decision-making.

  AstraZeneca comment: COVID-19 vaccination of breastfeeding mothers had minimal impact on breastfeeding. The vaccines used were not specified. No safety concerns were reported.

- Lechasa-Muniz et al 2021 analysed the presence of anti-SARS-CoV-2 antibodies in breast milk and serum (IgG and IgA) of vaccinated breastfeeding women. A total of 110 breastfeeding mothers were included; 70 women (63.6%) were vaccinated with two doses of

BNT162b2, 20 women (18.2%) with two doses of mRNA-1273, and 20 women (18.2%) with a single dose of ChAdOx1-S. When analysing IgG antibodies, significantly higher levels of antibodies were found in serum and breast milk from mothers vaccinated with BNT162b2 or mRNA-1273 vs. ChAdOx1-S ($p < 0.001$ and $p = 0.001$, respectively). Analysing IgA antibodies, significant differences were found when comparing mean values in serum from mothers vaccinated with BNT162b2 or mRNA-1273 vs. ChAdOx1-S (0.12, 0.16, and 0.02, respectively; $p < 0.001$) and breast milk of mothers vaccinated when comparing BNT16b2 vs. ChAdOx1-S. All vaccinated breastfeeding mothers had serum anti-S1 IgG antibodies in response to vaccination against SARS-CoV-2, regardless of the commercial vaccine administered. The authors concluded that anti-SARS-CoV-2 vaccines were well tolerated by the mothers and the breastfed infant. In addition, breastfeeding mothers offer their infants IgA and IgG isotype antibodies directed against SARS-CoV-2 protein S in breast milk.

AstraZeneca comment: This study is limited in its comparability of antibody levels amongst the different vaccines. At the time of the analyses women who received ChAdOx1-S vaccine received only one dose compared to two doses of the other vaccines. No safety concerns were reported.

There is no evidence of safety concerns relating to use of COVID-19 vaccines during breastfeeding in the literature articles presented.

The section 4.6 of the CDS for COVID-19 VACCINE ASTRAZENECA includes the following text on breastfeeding:

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with COVID-19 Vaccine AstraZeneca. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed. It is unknown whether the vaccine itself is excreted in human milk.

In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

During the Late-breaking period, Section 4.6 (Pregnancy and lactation) of the COVID-19 VACCINE ASTRAZENECA CDS was further updated to reflect current non-clinical, clinical and post-marketing data on the use of COVID-19 VACCINE ASTRAZENECA during breastfeeding (see Section 14).

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will continue to be considered missing information for AZD1222.

Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non-interventional pregnancy registry study (D8110C00003) of women exposed to COVID-19 VACCINE ASTRAZENECA immediately before or during pregnancy as part of the C-VIPER Registry Consortium. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.1.

16.3.5.2 Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency / Use in immunocompromised patients

Vaccines may be less effective in severely immunocompromised individuals, as the vaccinees weakened immune system may not mount a sufficient response. Additionally, immunocompromised individuals may also be at a greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population has been identified as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of COVID-19 VACCINE ASTRAZENECA in this population will be different than that of the general population, given the paucity of data, the possibility cannot be excluded.

Review of Cases

A cumulative and interval search of the AstraZeneca Global Safety Database was undertaken for AE reports received for COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency and in immunocompromised patients, using MedDRA High Level Term: Immune and associated conditions NEC.

Interval Period (29 June 2021 – 28 December 2021)

For the period covered by this report, a total of 3098 cases were identified from all sources using the above search strategy, including 84% spontaneous cases, 16% non-interventional/post-marketing cases, <1% literature, and <1% from the clinical study D8111C00003.

Of the 3098 cases, 71% of were reported in females and 26% were in males. Gender was not reported in the remaining 2% of cases. Age ranged from 0 to <18 years in <1% (8 cases), 18 years to <65 years in 74% (2278 cases) and 65+ Years in 19% (584 cases). The age group of adult, child, elderly and infant (age was not specified) was reported for 1% (18 cases). Age

was not reported in the remaining 7% (210) cases. The majority of reports 2616 (84%) were not medically confirmed with the remaining 482 (16%) being consumer reports.

Of these 3098 cases, 1557 (50%) were considered serious due to the AE being considered as medially important (1153), the AE resulted in disability (359), AE required hospitalization (404), AE was life threatening (44) and/or the AE resulted in death (38) Cases may have met more than one criteria for seriousness. The remaining 1541 (50%) reports were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 8969 events (68%) of the 13,190 events, of which 5143 events (39%) occurred within one day of vaccination, 1901 events (14%) occurred between 2-15 days post-vaccination, 1748 events (13%) occurred between 16-200 days post-vaccination,177 events (1%) occurred >200 days after vaccination and for the remaining 4221 events (32%) the time from vaccination to AE onset was unknown.

Outcome was reported for 3874 events (83%) of the 4660 events, with 1404 events (30%) reported as Recovered, 784 events (17%) as Recovering, 1498 events (32%) Not recovered, 150 events (3%) as Recovered with sequelae and unknown for 786 (17%) of reports. The outcome was fatal in 38 (<1%) of the total case count.

There were 38 deaths out of 3098 case reports reported during this period. Age of the 38 vaccinees with a fatal outcome ranged from 18 to 93 years with a median of 66 years. The reported PTs with a fatal outcome in the 38 cases in order of frequency (>6) were Cerebral haemorrhage (12), COVID-19 (12), Immune thrombocytopenia (12), Headache (10), Pulmonary embolism (10) and Dyspnoea (8). There were 26 cases were a fatal event occurred after 1st and 2 cases after 2nd dose. In 5 cases both doses were reported. There was limited information in the 5 case.

The top 20 reported PTs were Headache (836), Fatigue (656), Pyrexia (556), Chills (363), Myalgia (341), Arthralgia (325), Nausea (296), Pain in extremity (290), Malaise (231), Pain (213), Dizziness (203), Dyspnoea (159), Influenza like illness (148), Rash (118), Vomiting (118), Injection site pain (115), Diarrhoea (114), Asthenia (109), Pruritus (103) and Paraesthesia (94).

Nine cases were received from Clinical trial from the study D8111C00003, D8111C00004).Of these 9 cases (3 medically confirmed and 6 non medically confirmed), 7 cases were serious and 2 were non serious. Of these 9 cases, 8 were reported in female and 1 was reported in male. The reported PTs in order of frequency (>6) were Chills (14), COVID-19 (12), Maternal exposure during pregnancy (12), and Morning sickness (8).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca global safety database identified a cumulative total of 12019 cases from all sources, reported in subjects with severe immunodeficiency and in immunocompromised patients in association with COVID-19 VACCINE ASTRAZENECA, including 76.8% spontaneous cases, 23% non-interventional/post-marketing cases, <1% literature, <1% from the clinical studies D8111C0000) and <1% where the source was unknown.

Of the 12019 cases, 74% were reported in females, 23% were in males and gender was not reported in the remaining 3% of cases. Age ranged from 0 to 18 years in 37 cases (<1%) , between 18 years to <65 years in 9261 (77%) of the reports, 65+ Years in 1849 (15%), and 58 (<1%) age was not specified. Age was not reported in the remaining 6.77% (814) of cases. The majority of reports (88.61%) were not medically confirmed with the remaining 11.39% being consumer reports.

Of these 12019 cases, 8194 (68.17%) were considered serious due to the AE being considered as medially important (7016), the AE resulted in disability (1248), AE required hospitalization (885), AE was life threatening (309) and the AE resulted in death (88). Cases may have met more than one criteria for seriousness. The remaining 3825 (31.82%) reports were non serious.

Information on time to AE onset from vaccination was available for 36333 events of the 52985 events, with most 26751 (50.48%) occurred within one day of vaccination, 6434 (12.14%) occurred within 2-15 days post-vaccination, 2555 events (4.822%) occurred between 16-200 days post-vaccination, 593 events (1.119%) occurred >200 days after vaccination and for 16652 (31.427%) reports time from vaccination to AE onset was unknown.

Outcome was available for 97.32% of the 12019 cases, with 2700 (22.46%) reported as Recovered, 2475 (20.59%) as Recovering, 6188 (51.48%) Not recovered, 236 (1.96%) as Recovered with sequelae and unknown in 332 (2.76%) of reports. The outcome was fatal in 88 (0.73%) of the total case count.

Cumulatively there were 88 deaths out of 12019 case reports. Age of the 88 vaccinees with a fatal outcome ranged from 18to 96with a median of 66 years. The reported PTs with a fatal outcome in the 88 cases in order of frequency (>6) Dyspnoea (24), Cerebral haemorrhage (18), COVID-19 (18), Headache (18), Immune thrombocytopenia (18), Death (16), Myocardial infarction (16), Pulmonary embolism (14), Cerebrovascular accident (12), Cardiac arrest (10), Dysarthria (10), Photophobia (10), Adverse event following immunisation (9) Chest pain (9), Malaise (9), Thrombocytopenia (9), Cerebral venous sinus thrombosis (8), Peripheral swelling (8), Pneumonia (8), Thrombosis (8). There were 59cases were a fatal event occurred after 1st and in 7 cases – after 2nd dose. In 5 cases both doses were reported There was limited information in the 17 cases.

The top 20 reported PTs were Headache (4257), Pyrexia (3129), Fatigue (2942), Chills (2242), Nausea (1790), Myalgia (1649), Arthralgia (1445), Pain in extremity (1174), Dizziness (1170), Pain (935), Malaise (929), Vomiting (637), Influenza like illness (629), Dyspnoea (556), Rash (451), Injection site pain (420), Diarrhoea (572), Paraesthesia (422), Pruritus (451) and Asthenia (379).

Review of Cases: Clinical trial data: Ten cases were received from Clinical trial from the study D8111C00003, D8111C00004). Of these 10 cases (4 medically confirmed and 6 non medically confirmed) , 8 cases were serious and 2 were non serious. Of these 10 cases, 8 were reported in female and 2 was reported in male. The reported PTs in order of frequency (>6) were Chills (14), COVID-19 (12), Maternal exposure during pregnancy (12), Morning sickness (8).

Review of Cases from Literature: Sixteen cases were received from the literature. for COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency and in immunocompromised patients. Of these 16 cases (14 medically confirmed and 2 non-medically confirmed), 14 were serious and 2 were non serious. Of these 16 cases, 10 were reported in female and 6 were reported in male. The reported PTs in order of frequency (>6) were Immune thrombocytopenia (12), Dizziness (9) and Guillain-Barre syndrome (6).

Literature

A search of Embase and InsightMeme was conducted to identify literature articles on "Immune and associated conditions" disease' following the use of COVID-19 VACCINE ASTRAZENECA. The search identified 19 articles, out of which 7 literature articles were found to be relevant to the topic and have been discussed here in detail.

Terpos et al 2021 studied antibody responses in patients with Waldenstorm Macroglobulinemia (WM) after vaccination with BNT162b2 or AZD1222 vaccine. They concluded that vaccination with either 2 doses of the BNT162b2 or 1 dose of the AZD1222 vaccine led to lower production of neutralizing antibodies (NAbs) against SARS-CoV-2 in patients with WM compared with controls on days 22 and 50. Disease-related immune dysregulation and therapy-related immunosuppression are involved in the low humoral response. Importantly, active treatment with either rituximab or Bruton's tyrosine kinase inhibitors was proven as an independent prognostic factor for suboptimal antibody response after vaccination. Other factors associated with poor response were uncontrolled disease, immunosuppression, concomitant therapy, more lines of therapy and age. A US Food and Drug Administration–approved enzyme-linked immunosorbent assay–based methodology was implemented to evaluate NAbs on the day of the first vaccine shot, as well as on days 22 and 50 afterward. A total of 106 patients with WM (43% men; median age, 73 years) and 212 healthy controls (46% men; median age, 66 years) who were vaccinated during the same period at the same centre were enrolled in the study.

AstraZeneca comment: The author concluded that patients with WM have suboptimal production of anti–SARS-CoV-2 NAbs, in analogy to the response to influenza vaccines. Existing data on patients with plasma cell dyscrasias is rather limited and based on small and retrospective studies that suggest poor seroprotection rates of less than 20% after standard influenza vaccination. Treatment with rituximab or BTK inhibitors was an independent prognostic factor for suboptimal antibody response after vaccination.

Ludwig et al 2021 studied that patients with multiple myeloma frequently present with substantial immune impairment and an increased risk for infections and infection-related mortality. The risk for infection with SARS-CoV-2 virus and resulting mortality is also increased, emphasising the importance of protecting patients by vaccination. Available data in patients with multiple myeloma suggest a suboptimal anti-SARS-CoV-2 immune response, meaning a proportion of patients are unprotected. Factors associated with poor response are uncontrolled disease, immunosuppression, concomitant therapy, more lines of therapy, and CD38 antibody-directed and B-cell maturation antigen-directed therapy. In those who do not exhibit a good response, prophylactic treatment with neutralising monoclonal antibody cocktails might be considered. In patients deficient of a SARS-CoV-2 immune response, adherence to measures for infection risk reduction is particularly recommended. This consensus was generated by members of the European Multiple Myeloma Network and some external experts. The panel members convened in virtual meetings and conducted an extensive literature research and evaluated recently published data and work presented at meetings, as well as findings from their own studies. The European Myeloma Network for vaccination recommends that all patients with monoclonal gammopathy of unknown significance, smoldering multiple myeloma, multiple myeloma, and monoclonal gammopathies of clinical significance should be vaccinated with a COVID vaccine preferably before onset of active multiple myeloma or during well controlled disease at times of minimal residual disease negativity, complete response, or very good partial response or during periods without therapy or vaccination might be considered on individual judgment in patients with poorly controlled disease or ongoing therapy, but induction of protective immune response is less likely. Patients with previously confirmed COVID-19 infection should be vaccinated as well (one dose might be sufficient). In case of immune impairment, the network recommended administration of a third vaccine dose and infection risk reduction measures in insufficiently protected patients. It was also stated that immune impaired individuals would depend on herd immunity and would benefit from so-called ring vaccination of partners and close social contacts. Health-care personnel caring for patients with multiple myeloma and household members should be vaccinated.

AstraZeneca comment: The author suggested that monitoring the immune response to vaccination in patients with multiple myeloma might provide guidance for clinical management, such as administration of additional doses of the same or another vaccine, or

even temporary treatment discontinuation, if possible. No reference to a specific SARS-CoV-2 vaccine.

Hou et al 2021**,** studied the severity of SARS-CoV-2 infection is associated with the severity of chronic kidney disease (CKD) and kidney transplantation (KT) because of the chronic use of immunosuppressive agents. To develop adaptive immunity against SARS-CoV-2, vaccination against the spike protein is important. Current phase III trials of vaccines against SARS-CoV-2 have not focused on a specific group of individuals, such as patients with CKD or those undergoing dialysis or kidney transplantation. Chronic use of immunosuppressive agents might disturb the immune response to the SARS-CoV-2 spike protein. On the basis of limited evidence, the immune compromised status of CKD patients might decrease neutralizing antibody development after a single dose of a specific vaccine. Boosting dosage more than the protocol might increase the titre of the neutralizing antibody in CKD patients. Further evidence is needed to understand the factors disturbing the immunogenicity of the SARSCoV-2 vaccine, and CKD patients should receive the recommended dose of the SARS-CoV-2 vaccine due to their relatively immune compromised status. In CKD patients, the vitamin D deficiency, uremic toxin accumulation and erythropoietin deficiency could influence the antigen presenting ability of the antigen presenting cell (APC). In kidney transplantation (KT) patients, the corticosteroid, calcineurin inhibitor (tacrolimus or cyclosporin), mycopheloic acid (MPA) and mechanistic target of rapamycin (mTOR) inhibitor decrease the activity of T cells and the production of neutralizing antibody by B Cells in different aspects. The SARS-CoV-2 pandemic has posed a huge threat for CKD patients because of the higher risk of mortality in CKD and higher risk of the development of acute kidney injury. Beyond therapeutic agents, vaccines for the development of neutralizing antibodies against SARS-CoV-2 represent an important intervention for the prevention of critical illness in CKD patients.

AstraZeneca comment: The severity of CKD and the administration of immunosuppressive agents could influence the efficacy of SARS-CoV-2 vaccines. The use of antimetabolites might hamper the development of neutralizing antibodies. CKD patients should receive regular vaccinations and even booster doses during the SARS-CoV-2 pandemic. No reference to a specific SARS-CoV-2 vaccine.

Neurath et al 2021 conducted a review on immunosuppressive and biologic therapies for gastrointestinal diseases affecting the incidence or prognosis of COVID-19. The data focuses on the use of such therapies are discussed with a primary focus on inflammatory bowel disease, autoimmune hepatitis and liver transplantation. In particular, the roles of corticosteroids, classic immunosuppressive agents (such as thiopurines and mycophenolate mofetil), small molecules (such as Janus kinase (JAK) inhibitors), and biologic agents (such as tumour necrosis factor (TNF) blockers, vedolizumab and ustekinumab) are reviewed. Finally, the use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines for the

prevention of infection in patients with gastrointestinal diseases and concomitant immunosuppressive or biologic therapy will be discussed.

Initial data on COVID-19 in solid organ transplant (SOT) recipients receiving immunosuppressive therapy raised concerns that this infection might lead to high mortality. A study of 36 kidney transplant recipients receiving immunosuppressive therapy demonstrated lower $CD4^+$ and $CD8^+$ T cell counts in peripheral blood. Furthermore, more-rapid clinical progression of disease was observed compared with the general population, indicating a high early mortality rate among kidney transplant recipients (28% at 3 weeks). A second study of 778 SOT recipients (including 110 liver transplant recipients) in Spain found that the incidence of COVID-19 in SOT recipients was twofold higher than in the general population; 89% of patients with COVID-19 were admitted to hospital, whereas adjustment of immunosuppression was performed in 85%. Overall, 27% of SOT recipients diagnosed with COVID-19 died and univariate analysis yielded lung transplantation and hospital-acquired COVID-19 infection as risk factors for death. A third study in 18 transplant recipients (44% kidney, 33% liver, 22% heart) with COVID-19 reported a case-fatality rate of 27%, suggesting that SARS-CoV-2 infection results in a severe course of COVID-19 in many transplant recipients. Similarly, in a study of 11 SOT (kidney and liver) recipients with HIV, there was a high mortality rate of 36%. By contrast, a study of 21 SOT recipients diagnosed with COVID-19 demonstrated favourable short-term outcomes, with less than 10% mortality, but highlighted that 50% required treatment at intensive care units and that those with concomitant infections had more severe illness. Finally, a Spanish observational study in 46 adult SOT recipients with SARS-CoV-2 infection reported a higher mortality in SOT recipients compared with matched controls (37 versus 23%). In this study, 72% of patients underwent transitory discontinuation of immunosuppressants due to potential or confirmed drug–drug interactions. Potential concerns included the possibility of drug–drug interactions between tacrolimus and some of the treatments with antiviral effects such as lopinavir-ritonavir and azithromycin.

Chronic immunosuppression could exert a protective effect against the severe forms of COVID-19, arguing against complete withdrawal of immunosuppression in liver transplant recipients. Unlike calcineurin inhibitors, mycophenolate mofetil might facilitate COVID-19 and should be used cautiously unless further studies become available.

In patients with IBD, high-dose corticosteroid treatment before SARS-CoV-2 infection has been identified as a key risk factor for aggravated outcomes, suggesting that corticosteroid therapy for IBD in general should be reduced or avoided if possible. Non-glucocorticoid immunosuppression in patients with IBD and liver transplant recipients per se appears not to be a risk factor for aggravated outcomes and could even exert a protective effect against the most severe forms of COVID-19. Therefore, complete withdrawal of immunosuppression is not advisable. Studies in liver transplant recipients have additionally highlighted the potential

benefits of tacrolimus therapy, whereas one study described the potentially deleterious effects of mycophenolate therapy. These results should be considered in attempts to modulate immunosuppression in liver transplant recipients during COVID-19, but they require further confirmatory studies.

AstraZeneca comment: More data on efficacy are clearly needed as patients with immune-mediated inflammatory diseases have not been studied in detail in the clinical trials. Antibody responses in these patients should be closely monitored as concomitant immunosuppressive or biologic therapy might affect T cell immunity and antibody production by B cells.

In Parry et al 2021, studied the spike-specific antibody responses following first and/or second COVID-19 vaccination in 299 patients with chronic lymphocytic leukaemia (CLL) compared with healthy donors. 286 patients underwent extended interval (10-12 week) vaccination. 154 patients received the BNT162b2 mRNA vaccine, and 145 patients received ChAdOx1. Blood samples were taken either by venepuncture or as dried blood spots on filter paper. Spike-specific antibody responses were detectable in 34% of patients with CLL after one vaccine (n = 267) compared to 94% in healthy donors with antibody titres 104-fold lower in the patient group. Antibody responses increased to 75% after second vaccine (n = 55), compared to 100% in healthy donors, although titres remained lower. Multivariate analysis showed that current treatment with BTK inhibitors or IgA deficiency were independently associated with failure to generate an antibody response after the second vaccine. This work supports the need for optimisation of vaccination strategy in patients with CLL including the potential utility of booster vaccines.

AstraZeneca comment: The author concluded that patients with CLL should be considered for early delivery of the second vaccine. However, antibody responses may remain suboptimal even after two vaccines. One option might be to consider a third 'booster' vaccine and this is being implemented in some countries for patients in other risk groups. At this stage it is not clear if a third vaccine will indeed act to further boost antibody responses although the substantial increment after the second boost and the high antibody titres observed following natural infection suggest that this may be possible. It is possible that vaccination may serve to provide sufficient 'immune-priming' to protect against severe disease from subsequent infection even in the absence of a measurable spike-specific antibody response.

In Larsen et al 2021 investigated the immune response during a 24-month follow-up period in patients with Systemic Lupus Erythematosus (SLE) following COVID-19 vaccination with a two-dose regimen. Patients with SLE (≥18 years of age) in the Region of Southern Denmark were invited to participate in the study. Blood samples were drawn approximately 3 weeks after the first vaccination and 4 and 8 weeks after the second vaccination. SLEDAI-score and SLICC damage were assessed between vaccinations and 8 weeks after the second vaccination. Patients' hospital records were reviewed for clinical information and treatment data. Patients

with SLE had a good antibody response after COVID-19 vaccination, without secondary flare of disease activity.

AstraZeneca comment: Patients with SLE show reduced immunogenicity against influenza and pneumococcal vaccination, however the immune response depends on immunosuppressive therapy and disease activity.

Yen et al 2021 discussed COVID- vaccines in patients with maintenance hemodialysis (MHD). Patients with MHD have a greater risk of COVID-19 infection owing to their comorbidities, defective immunity, and repeated crowded in-center dialysis settings. Overall, lower and more delayed antibody responses following COVID-19 vaccination were observed in patients with MHD than in healthy controls in the settings of different populations, vaccines and dosage, definitions of the immune response, and antibody detection timepoints. Younger age, previous COVID-19 infection, and higher serum albumin level were positively associated with antibody formation, whereas older age and receiving immunosuppressive therapy were unfavorable factors. Patients with MHD should make their COVID-19 vaccination a priority in addition to other protective measures.

AstraZeneca comment: More studies focusing on different vaccines, non-humoral immune responses, and risk-benefit analyses are warranted.

Summary

This review presented the cumulative and periodic data in subjects with severe immunodeficiency and in immunocompromised patients, using MedDRA High Level Term: Immune and associated conditions NEC.

Cumulatively a total of 12019 reports and 3098 cases were reported during the interval period, with the majority (74% cumulatively and 71% for the reporting interval) of cases concerning females. The vast majority of reports (88.61% cumulatively and 84% in the reporting interval) were not medically confirmed.

Cumulatively 68.17% of cases were serious and 88 cases had a fatal outcome, out of which 38 were reported in the interval period, with a median age of patients who died 66 years old. Cumulatively there were 59 serious cases were a fatal event occurred after the 1st and in 7 cases – after 2nd dose of vaccine. In 5 cases both doses were reported. There was limited information in the 17 cases. Also, no abnormal trends or significant safety concerns were identified in the interval period with respect to the cumulative period.

The review and analysis of the available literature did not highlight any particular safety concerns with COVID-19 VACCINE ASTRAZENECA when used in immunocompromised

patients. There were no articles identified with a specific reference to any new safety concerns associated with COVID-19 VACCINE ASTRAZENECA.

Conclusion

This cumulative and periodic review of the Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any safety concerns. Overall, the review of the available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency/Use in immunocompromised patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to AZD1222. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.2.

16.3.5.3 Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and / or uncontrolled underlying disease / Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)

Subjects with severe and/or uncontrolled underlying diseases are potentially at risk of developing a more severe manifestation of COVID-19 and, as a consequence, have been included as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of COVID-19 VACCINE ASTRAZENECA in this population will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Indicators of frailty used in the review of cases were defined in the protocol for the COVID-19 VACCINE ASTRAZENECA PASS: A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data sources. This protocol was approved by EMA on 27 January 2022, post data-lock point for this PSUR. As no follow-up questionnaires are sent for this missing information concept, no scale of frailty was used for the assessment of the spontaneous cases. Rather, a case narrative text search of COVID-19 VACCINE ASTRAZENECA reports in the AstraZeneca global safety database using the parameters for each indicator of frailty in Table 157 was used to identify cases for review in the sub-sections below:

Table 157 Indicators of Frailty

Frailty Indicator	Search Parameter
Frailty	- "Frailty" - "Bedridden"
Dispensing of or reimbursement for durable medical equipment (eg, wheelchairs, home oxygen)	- "oxygen" - "O2" - "scooter" - "walker" - "wheelchair" - "wheel-chair"
Residence in long-term facility or nursing home	- "long term" - "nursing home" - "skilled care" - "skilled-care"
Hip fracture	- "hip fracture" - "fractured hip" - "broken hip" - "hip broken"
Palliative care	- "palliative" - "hospice" - "palliate"
Metastatic cancer	- "metastatic" - "metastasis" - "metastases" - "metastasise" - "cancer spreading" - "cancer spread"
Cachexia	- "cachexia" - "wasting" - "waste"
Dementia	- "dementia" - "Alzheimer" - "memory" - "cognitive" - "cognition"
Pressure ulcers	- "ulcer"
Bladder incontinence	- "bladder" - "urine" - "leak"

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database through 28 December 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail. All the categories are described below:

16.3.5.3.1 Frailty

Interval Period (29 June 2021 – 28 December 2021)

The search identified 30 spontaneous case reports in frail vaccinees who received COVID-19 VACCINE ASTRAZENECA.

Of the 30 cases, 20 (66.7%) were reported in females, 9 (30.0%) in males and gender was not reported in the remaining 1 (3.3%) case. Age ranged from 18 years to <65 years in 13.3% of the reports; 65+ years in 83.3% and age was not reported in the remaining 3.3% of cases. The half of reports 15 (50.0%) were from consumers with the remaining 50.0 % being medically confirmed.

Of these 30 cases, 27 (90.0%) were serious due to AE being considered as medially important (18), AE resulted in disability (5), AE required hospitalization (8), AE was life threatening (3), and AE resulted in death (14). Cases may have met more than one criteria for seriousness. The remaining 3 (10.0%) reports were non serious.

The time to onset from vaccination to the event was available for (86.8% (33 events) of the 30 cases, of which 18.4% occurred within 1 day of vaccination, 34.2% occurred within 2-15 days post-vaccination, 31.6% occurred between 16-200 days post-vaccination, 2.6% occurred >200 days after vaccination and for 13.2% events time from vaccination to AE onset was unknown.

Outcome was available for 65.7% (90 events) of the 30 cases, with 7.7% reported as Recovered, 9.6% as Recovering, 30.8% Not recovered, 1.9% as Recovered with sequelae and unknown in 23.1% of reports. The outcome was fatal in 14 (26.9%) of the total case count.

Of the 30 reports, there were 14 cases with fatal outcome reported during this period. Age of the 14 vaccinees who died ranged from 67 to 97 years with a median of 83 years. The reported PTs in the 14 cases with a fatal outcome in order of frequency (>6) were as follows: Pulmonary embolism (25), Hepatic cirrhosis (20), Asthenia (19) and Abdominal distension (11). There were 9 cases were a fatal outcome occurred after 1st dose of vaccine and 1 case – after 2nd dose. In 2 cases both doses were reported; in 1 case 3rd dose was reported and in 1 case the dose was unknown.

The top 20 reported PTs were Asthenia (6), Malaise (6), Nausea (4), Pulmonary embolism (4), Pyrexia (4), Deep vein thrombosis (3), Peripheral swelling (3), Vomiting (3), Abdominal distension (2), Arrhythmia (2), Death (2), Diarrhoea (2), Oedema peripheral (2), Pain in extremity (2), Rash (2), Abdominal pain (1), Abdominal pain upper (1), Abnormal weight gain (1), Acute left ventricular failure (1), Amnesia (1). Of the AEs reviewed within the 30 reports, 20 reports contained adverse events that were considered associated with the underlying frail condition.

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca global safety database identified a cumulative total of 659 cases (98.0% spontaneous cases, 2.0% non-interventional/post-marketing cases) for the topic use of COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Indicators of frailty_frail.

Of the 659 cases, 515 (78.15%) of were reported in females, 120 (18.20%) - in males and gender was not reported in the remaining 24 (3.64%) of cases. Age ranged from 18 years to <65 years in 56.7% of the reports; 65+ years in 30.8% and age was not reported in the remaining 12.4% of cases. The majority of reports (77.7%) were not medically confirmed with the remaining 22.3% being consumer reports.

Of these 659 cases, 389 (59.0%) were serious due to the AE being considered as medially important (271), AE resulted in disability (97), AE required hospitalization (54), AE was life threatening (23), and the AE resulted in death (86). Cases may have met more than one criteria for seriousness. The remaining 270 (41.0%) reports were non serious.

The time to onset from vaccination to the event was available for 69.0% (496 events) of the 659 cases. Most of the events (51.6%) occurred within 1 day of vaccination, 11.3% occurred within 2-15 days post-vaccination, 5.8% occurred between 16-200 days post-vaccination, 0.3% occurred >200 days after vaccination and for 31% of events time from vaccination to AE onset was unknown.

Outcome was reported for 76.0% (876 events) of the 659 cases, with 30.0% reported as Recovered, 16.4% as Recovering, 19.3% Not recovered, 2.9% as Recovered with sequelae and unknown in 24.0% of reports. The outcome was reported as fatal for 86 (7.5%) of the total case count, of which 14 cases with fatal outcome were reported during the interval period, as described above.

The top 20 reported PTs were Bedridden (468), Headache (284), Pyrexia (271), Fatigue (209), Nausea (186), Chills (185), Myalgia (123), Dizziness (121), Pain (118), Malaise (117), Asthenia (108), Arthralgia (104), Pain in extremity (83), Vomiting (77), Decreased appetite

(70), Dyspnoea (59), Hyperhidrosis (51), Diarrhoea (49), Influenza like illness (49), and Death (43).

16.3.5.3.2 Hip Fracture

Search Strategy

A cumulative and periodic search of the global safety database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title Hip fracture.

Interval Review (29 June 2021 – 28 December 2021)

The search identified 5 case reports in frail vaccinees with hip fracture who received COVID-19 VACCINE ASTRAZENECA and all cases were spontaneously reported. Of the 5 cases, 80.0% (4) of were reported in females and 20.0% (1) were in males. Age ranged from 18 years to <65 years in 20.0% of the reports and 65+ years in 80.0%. The half of reports (50.0%) were not medically confirmed with the remaining 50.0 % being consumer reports.

Of these 5 cases, 4 (80.0%) were serious due to AE being considered as medially important (2), AE resulted in disability (2), AE required hospitalization (2). Cases may have met more than one criteria for seriousness. The remaining 1 (20.0%) report was non-serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 83.3% (5 events) of the 5 cases, with 33.3% occurred within 1 day of vaccination, 16.7% occurred within 10-15 days post-vaccination, 33.3% occurred between 16-20 days post-vaccination and for 16.7% of events time from vaccination to AE onset was unknown.

Outcome was reported in 100% of the cases, with 40.0% (2) reported as Recovered, 20% (1) as Recovering and for remaining 40.0% (2) cases Not recovered. There were no fatal cases reported in individuals with hip fracture during the interval.

The reported PTs were Acute disseminated encephalomyelitis, Arthralgia, Cerebrovascular accident, Deep vein thrombosis, Dysarthria, Dyspnoea, Headache, Pain, Pulmonary embolism, Pyrexia, Retinal artery occlusion, Swelling, Thrombocytopenia and Thrombosis (each n=1).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 23 spontaneous cases for the topic use of COVID-19 VACCINE ASTRAZENECA in individuals with hip fracture.

Of the 23 cases, 78.3% (18 cases) were reported in females and 21.7% (5 cases) were in males. Age ranged from 18 years to <65 years in 34.8% of the reports, 65+years in 65.2%. The majority of reports (73.9%) were from consumers with the remaining 26.1% being medically confirmed.

Of these 23 cases, 16 (69.6%) were serious due to AE being considered as medially important (11), AE resulted in disability (4), AE required hospitalization (6), AE was life threatening (1), and AE resulted in death (3). Cases may have met more than one criteria for seriousness. The remaining 7 (30.4%) reports were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 84% (21 events) of the 23 cases. Most of the events (52.0%) occurred within 1 day of vaccination, 20% (5 events) occurred within 2-15 days post-vaccination, 12% occurred between 16-20 days post-vaccination and in 16% time from vaccination to AE onset was unknown.

Outcome was available for 76.3% of the 29 cases, with 26.3% reported as Recovered, 7.5% as Recovering, 33.8% Not recovered and unknown in 23.8% of cases. The outcome was reported as fatal in 7 (8.8%) of the total case count.

The top 20 reported PTs were Headache (8), Fatigue (5), Pyrexia (5), Chills (3), Pulmonary embolism (3), Arthralgia (2), Deep vein thrombosis (2), Diarrhoea (2), Dyspnoea (2), Malaise (2), Myalgia (2), Nausea (2), Pain in extremity (2), Thrombocytopenia (2), Vomiting (2), Abdominal pain (1), Abdominal pain upper (1), Acute disseminated encephalomyelitis (1), Asthenia (1) and Balance disorder (1).

16.3.5.3.3 Cachexia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title Cachexia.

Interval Review (29 June 2021 – 28 December 2021)

The search identified 101 spontaneous case reports in cachexic individuals who received COVID-19 VACCINE ASTRAZENECA.

Out of 101 cases, 58.4% (59) were reported in females, 39.6% (40) in males and gender was not reported in the remaining 2.0% (2) of cases. Age ranged from 18 years to <65 years in 78.2% (78 cases); 65+ years in 14.9% (15 cases) and age was not reported in the remaining

6.9% (7 cases). Majority of reports 77.2% (78 cases) were from consumers, with the remaining 22.8% (23 cases) being medically confirmed.

Of these 101 cases, 66 (65.3%) were serious due to AE being considered as medially important (28), AE resulted in disability (15), AE required hospitalization (35), AE was life threatening (6), and AE resulted in death (4). Cases may have met more than one criteria for seriousness. The remaining 35 (34.7%) reports were non serious.

Information on time to event onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 67.6% (73 events) of the 101 cases, with 37.0% occurred within 1 day of vaccination, 20.4% occurred within 2-15 days post-vaccination, 10.2% occurred between 16-200 days post-vaccination and for 32.4% reports time to onset was unknown.

Outcome was available for 76.6% (128 events) of the cases, with 25.7% reported as Recovered, 14.4% as Recovering, 1.8% Recovered with Sequelae,32.2% Not recovered and unknown in 23.4%. Outcome was reported as fatal in 2.4% (4) cases.

Of the 101 reports, there were 4 cases with fatal outcome reported during this period. Age of the vaccinees with a fatal outcome ranged from 61 to 90 years with a median of 76 years. The reported PTs in the 4 cases with a fatal outcome in order of frequency (>2) were as follows: Death (4), Cachexia (3), Dyspnoea (3), Fatigue (3), Lung cancer metastatic (3), Lung neoplasm malignant (3), Malignant neoplasm of unknown primary site (3), Poisoning (3), Respiratory failure (3).There was 1 case were a fatal outcome occurred after 1st dose of vaccine and 1cases – after 2nd dose. There was limited information 2 in the cases.

The reported PTs for the remaining AEs were Headache (36), Muscular weakness (25), Pyrexia (25), Fatigue (24), Myalgia (20), Dizziness (17), Chills (14), Muscle atrophy (12), Malaise (11), Asthenia (10), Influenza like illness (10), Pain in extremity (10), Nausea (9), Pain (9), Arthralgia (8), Dyspnoea (8), Hypoaesthesia (8), Paraesthesia (8), Tachycardia (7) and Vomiting (7).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 180 cases (99.4% spontaneous cases and 0.6% non-interventional/post-marketing) in individuals identified through a Standard Search Query for the report title Cachexia.

Of the 180 cases, 58.3% (105 cases) were reported in females, 38.3% (69 cases) in males and gender was not reported in the remaining 3.3% (6) of cases. Age ranged from 18 years to <65 years in 72.8% (130) of the reports; 65+ years in 18.3% (33); 0.6% (1 case) was reported in adult population. Age was not reported in the remaining 8.9% (16) of cases. The majority of

reports 77.2% (139) were from consumers, with the remaining 22.8% (41) cases being medically confirmed.

Of these 180 cases, 130 (64.4%) were serious due to AE being considered as medially important (74), AE resulted in disability (20), AE required hospitalization (47), AE was life threatening (12), and AE resulted in death (7). Cases may have met more than one criteria for seriousness. The remaining 72 (35.6%) reports were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 73.7% (140 events) of the 180 cases. Most of the events (47.9%) occurred within 1 day of vaccination, 17.4% occurred within 2-15 days post-vaccination, 8.4% occurred between 16-200 days post-vaccination and for 26.3% events time from vaccination to AE onset was unknown.

Outcome was available for 76.0% of the 180 cases, with 25.3% reported as Recovered, 13.7% as Recovering, 31.7% Not recovered, 3.0% as Recovered with sequelae and unknown for 24.0% of reports. Outcome was reported as fatal for 7 (2.3%) cases, of which 4 were reported during the interval period, as described in the previous section.

The top 20 reported PTs were: Headache (56), Fatigue (45), Pyrexia (43), Muscular weakness (30), Dizziness (28), Myalgia (27), Muscle atrophy (26), Chills (25), Pain (18), Pain in extremity (18), Influenza like illness (17), Malaise (17), Nausea (17), Arthralgia (16), Asthenia (15), Vomiting (14), Hypoaesthesia (12), Paraesthesia (12), Diarrhoea (11), and Dyspnoea (11).

16.3.5.3.4 Bladder Incontinence

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title Bladder incontinence.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 1399 case reports in individuals with underlying bladder incontinence who received COVID-19 VACCINE ASTRAZENECA (93.5% spontaneous cases, 4.1% non-interventional/post-marketing, 2.3% literature and 0.1% each from the study ChAdOx1 nCoV-19_ZA_phI/II and COV002).

Of the 1399 cases, 66.1% (925) were reported in females, 32.0% (447) in males and gender was not reported in the remaining 1.9% (27) of cases. Age ranged from 0 to <18 years in 0.1% (1 case) of the reports, 18 to <65 years in 65.8% (921), 65+ years in 25.4% (355) cases; in

0.7% (10) cases reported adult and elderly and age was not reported in the remaining 8.0% (112 cases). The majority of cases 78.4% (1097) were consumer reports with the remaining 21.6% (302) cases being medically confirmed.

Of these 1399 cases, 915 (65.4%) were serious due to AE being considered as medially important (659), AE resulted in disability (169), AE required hospitalization (398), AE was life threatening (91), and AE resulted in death (67). Cases may have met more than one criteria for seriousness. The remaining 484 (34.6%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 70.3% (1147 events) of the 1399 cases. Most of the events (32.1%) occurred within 1 day of vaccination, 18.8% occurred within 2-15 days post-vaccination, 18.1% occurred between 16-200 days post-vaccination, 1.2% over 1 year and for 29.7% of events time from vaccination to AE onset was unknown.

Outcome was reported for 77.1% of the 1399 cases, with 24.2% reported as Recovered, 17.8% as Recovering, 28.8% Not recovered, 3.3% as Recovered with sequelae and unknown in 22.9% of reports. The outcome was reported as fatal in 67 (2.9%) of the total case count.

Of the 1399 reports, there were 67 cases with fatal outcome reported during this period. Age of the 67 vaccinees with a fatal outcome ranged from 23 to 98 years with a median of 66.5 years. The reported PTs in the 67 cases with a fatal outcome in order of frequency (>10) were as follows: Death (61), Pulmonary embolism (25), Cerebrovascular accident (19), Septic shock (17), Acute kidney injury (12) and Epilepsy (12). There were 36 cases where a fatal event occurred after 1st dose of vaccine and 8 cases – after 2nd dose. In 9 cases both dose were reported. There was limited information in 14 cases.

The top 20 reported PTs were Headache (332), Pyrexia (282), Fatigue (281), Nausea (166), Chills (165), Myalgia (148), Arthralgia (137), Dizziness (132), Pain (131), Pain in extremity (131), Malaise (125), Dyspnoea (103), Asthenia (92), Paraesthesia (90), Abdominal pain (87), Blood urine present (74), Vomiting (73), Diarrhoea (67), Chest pain (65), Chromaturia (65).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 4085 cases (96.32% spontaneous cases, 2.76% non-interventional/post-mark pet, 0.807% from literature and 0.073% from the study ChAdOx1 nCoV-19_ZA_phI/II, COV002, D8110C00001 and ICMR/SII-AZD-COVID-19/2020) in individuals with underlying bladder incontinence.

Of the 4085 cases, 67.9% (2773) were reported in females, 29.8% (1219) in males and gender was not reported in the remaining 2.3% (93) of cases. Age ranged from 0 to <18 years in 0.1%

(3) of the reports; 18 to <65 years in 65.7% (2682) cases, 65+ years in 25.9% (1056) and age was not reported in the remaining 7.6% (311) of cases. The age group of adolescent, adult and elderly (age was not specified) was reported for 0.8% (33) cases. The majority of reports (84.4%) were from consumers with the remaining 15.6% being medically confirmed.

Of these 4085 cases, 2962 (72.5%) were serious due to AE being considered as medially important (2377), AE resulted in disability (459), AE required hospitalization (744), AE was life threatening (205), and AE resulted in death (130). Cases may have met more than one criteria for seriousness. The remaining 1123 (27.5%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 78.8% (3477 events) of the 4085 cases. Most of the events (49.1%) occurred within 1 day of vaccination, 18.3% occurred within 2-15 days post-vaccination, 10.7% occurred between 16-20 days post-vaccination, 0.7% over 1 year and for 21.2% events time from vaccination to AE onset was unknown.

Outcome was reported for 78.3% of the 4085 cases, with 26.3% reported as Recovered, 21.2% as Recovering, 26.3% Not recovered, 2.8% as Recovered with sequelae and unknown in 21.7% of reports. Outcome was reported as fatal in 130 (1.8%) of the total case count, of which 67 cases with fatal outcome were reported during the interval period, as described in the previous section.

The top 20 reported PTs were Headache (1,231), Pyrexia (992), Fatigue (896), Chills (654), Nausea (620), Myalgia (441), Arthralgia (431), Dizziness (426), Pain in extremity (406), Malaise (367), Pain (364), Vomiting (276), Dyspnoea (251), Diarrhoea (248), Abdominal pain (220), Paraesthesia (219), Asthenia (209), Back pain (202), Hyperhidrosis (199) and Influenza like illness (197).

16.3.5.3.5 Dementia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title AZD1222_Dementia.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 951 case reports (97.5% spontaneous, 1.9% non-interventional/post-market and 0.6% literature) in individuals with underlying dementia who received COVID-19 VACCINE ASTRAZENECA.

Of the 951 cases, 64.9% (617) were reported in females, 32.3% (307) in males and gender was not reported in the remaining 2.8% (27) of cases. Age ranged from 18 to <65 years in 56.6% (538); 65+ years in 32.6% (310) and age was not reported in the remaining 9.9% (94) of cases. The age group of adult and elderly (age was not specified) was reported for 0.9% (9 cases). The majority of reports 754 (79.3%) were from consumers, with the remaining 20.7% (197) cases being medically confirmed.

Of these 951 cases, 666 (70.0%) were serious due to AE being considered as medially important (436), AE resulted in disability (221), AE required hospitalization (261), AE was life threatening (83), and AE resulted in death (53). Cases may have met more than one criteria for seriousness. The remaining 285 (30.0%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 67.3% (738 events) of the 951 cases. Most of the events (32.8%) occurred within 1 day of vaccination, 16.8% occurred within 2-15 days post-vaccination, 16.8% occurred between 16-200 days post-vaccination, 1.0% up to 1 year and for 32.7% events time from vaccination to AE onset was unknown.

Outcome was available for 78.9% (1311 events) of the 951 cases, with 18.2% reported as Recovered, 17.3% as Recovering, 35.2% Not recovered, 5.1% as Recovered with sequelae and was unknown in 21.1% of reports. Outcome was reported as fatal in 53 (3.2%) of the total case count.

Of the 951 reports, there were 53 cases with fatal outcome reported during this period. Age of the 53 vaccinees with a fatal outcome ranged from 34 to 98 years with a median of 81 years. The reported PTs in the 53 cases with a fatal outcome in order of frequency (>6) were: Death (13), Pneumonia (9), Pulmonary embolism (8), Thrombocytopenia (8), Amnesia (7), Cerebrovascular accident (7). There were 28 cases were a fatal outcome occurred after 1st dose of vaccine and 4 cases – after 2nd dose. In 9 cases both doses were administered. There was limited information in 12 cases.

The top 20 reported PTs were Headache (325), Fatigue (309), Memory impairment (296), Amnesia (237), Dizziness (181), Cognitive disorder (154), Pyrexia (149), Disturbance in attention (129), Confusional state (115), Myalgia (111), Arthralgia (104), Nausea (97), Dyspnoea (93), Asthenia (91), Malaise (89), Chills (78), Pain (73), Paraesthesia (67), Feeling abnormal (61) and Pain in extremity (60).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 2327 cases (98.02% spontaneous, 1.63% non-interventional/post-marketing, 0.26% from literature

and 0.085% from the study D8110C00001 and ICMR/SII-AZD-COVID-19/2020) in individuals with dementia who received COVID-19 VACCINE ASTRAZENECA

Of the 2327 cases, 65.3% (1520) were reported in females, 32.4% (755) in males and gender was not reported for the remaining 2.2% (52) of cases. Age ranged from 0 to <18 years in 0.1% (2) of the reports; 18 to <65 years in 51.7% (1204), 65+ years in 38.5% (897) and age was not reported in the remaining 8.5% (198) of cases. The age group of adolescent, adult and elderly (age was not specified) was reported for 26 (1.1%) cases. The majority of reports 1807 (77.7%) were from consumers with the remaining 520 cases (22.3%) being medically confirmed.

Of these 2327 cases, 1781 (76.5%) were serious due to the AE being considered as medially important (1234), AE resulted in disability (463), AE required hospitalization (515), AE was life threatening (184), and AE resulted in death (168). Cases may have met more than one criteria for seriousness. The remaining 546 (23.5%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 73.9% (1859 events) of the 2327 cases. Most of the events (43.9%) occurred within 1 day of vaccination, 17.9% occurred within 2-15 days post-vaccination, 11.4% occurred between 16-20 days post-vaccination, 0.7% over 1 year and for 26.1% events time from vaccination to AE onset was unknown.

Outcome was reported for 80.0% of the 2327 cases, with 22.0% as Recovered, 19.2% as Recovering, 30.0% Not recovered, 4.7% as Recovered with sequelae and unknown in 20.0% of reports. Outcome was reported as fatal in 168 (4.0%) of the total case count, of which 53 cases with fatal outcome were identified during the reporting period, as described in the previous section.

The top 20 reported PTs were Headache (731), Fatigue (687), Amnesia (566), Memory impairment (545), Pyrexia (420), Dizziness (370), Cognitive disorder (327), Confusional state (306), Nausea (273), Chills (261), Myalgia (260), Arthralgia (233), Malaise (211), Disturbance in attention (210), Dyspnoea (191), Asthenia (173), Pain in extremity (157), Pain (154), Feeling abnormal (130) and Paraesthesia (124).

16.3.5.3.6 Long term Frailty

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title Indicators of frailty_long term.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 316 case reports in individuals with long term frailty who received COVID-19 VACCINE ASTRAZENECA (97.15% spontaneous cases,0.949% non-interventional/post-marketing and 1.58% literature).

Of the 316 cases, 58.2% (184) were reported in females, 39.9% (126 cases) in males and gender was not reported in the remaining 1.9% (6) of cases. Age ranged from 0 to <18 years in 0.3% (1 case); 18 to <65 years in 68.4% (216) cases; 65+ years in 21.5% (68) cases and age was not reported in the remaining 8.9% (28) of cases. The age group of adult (age not specified) was reported for 0.9% cases. The majority of reports 275 (87.0%) were from consumers with the remaining 41 cases (13.0%) being medically confirmed.

Of these 316 cases, 284 (89.9%) were serious due to AE being considered as medially important (193), AE resulted in disability (69), AE required hospitalization (126), AE was life threatening (47), and AE resulted in death (24). Cases may have met more than one criteria for seriousness. The remaining 32 (10.1%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 72.7% (277 events) of the 316 cases, with 24.4% of events occurred within 1 day of vaccination, 24.9% occurred within 2-15 days post-vaccination, 22.8% occurred between 16-200 days post-vaccination, 0.5 % up to 1 year and for 27.3% events time from vaccination to AE onset was unknown.

Outcome was reported for 74.6% (277 events) of the 316 cases, with 17.8% reported as Recovered, 18.2% as Recovering, 29.4% Not recovered, 5.0% as Recovered with sequelae and unknown in 25.4% of reports. Outcome was reported as fatal for 24 (4.2%) of the total case count.

Of the 316 reports, there were 24 cases with fatal outcome reported during this period. Age of the 24 vaccinees who died ranged from 33 to 8 years with a median of 70 years. The reported PTs in the 24 cases with a fatal outcome in order of frequency (>6): Death (30), Concomitant disease progression (12), Pneumonia (10), and Pulmonary embolism (7).There were 10 cases were a fatal event occurred after 1st dose of vaccine and 1 case – after 2nd dose. In 2 cases both doses were reported. There was limited information in 11 cases.

The top 20 reported PTs were Headache (720), Fatigue (61), Paraesthesia (45), Pain in extremity (42), Hypoaesthesia (38), Pyrexia (36), Dyspnoea (35), Pain (32), Malaise (31), Arthralgia (30), Nausea (30), Dizziness (29), Chest pain (27), Guillain-Barre syndrome (26), Muscular weakness (22), Myalgia (21), Chills (20), Asthenia (19), Influenza like illness (18) and Palpitations (18).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca global safety database identified a cumulative total of 675 cases (98.07% spontaneous, 1.03% non-interventional/post-marketing, 0.74% literature and 0.14% from study COV002) in individuals with long term frailty.

Of the 675 cases, 63.3% (427) were reported in females, 34.4% (232) in males and gender was not reported in the remaining 2.4% (16 cases). Age ranged from 0 to <18 years in 0.1% (1 case); 18 years to <65 years in 65.2% (440) and 65+ years in 24.1% (163) cases. The age group of adult and elderly (age not specified) was reported for 1.2% cases. Age was not reported for the remaining 9.3% (63) of cases. The majority of reports 582 (86.2%) were from consumers with the remaining 93 (13.8%) being medically confirmed.

Of these 675 cases, 626 (92.7%) were serious due to AE being considered as medially important (460), AE resulted in disability (140), AE required hospitalization (185), AE was life threatening (74), and AE resulted in death (54). Cases may have met more than one criteria for seriousness. The remaining 49 (7.3%) reports were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 78.3% (592 events) of the 675 cases. Most of the AEs 39.7% (300) occurred within 1 day of vaccination, 22.4% (169) occurred within 2-15 days post-vaccination, 15.9% (120) occurred between 16-200 days post-vaccination, 0.4% (3) occurred over 200 days to 1 year after vaccination and for 21.7% (164) time from vaccination to AE onset was unknown.

Outcome was reported for 77.2% (1008 events) of the 675 cases, with 20.5% (268 events) reported as Recovered, 20.2% (264 events) as Recovering, 27.7% (362 events) Not recovered, 4.6% (60 events) as Recovered with sequelae and unknown in 22.8% (297 events). Outcome was reported as fatal in 54 (4.1%) of the total case count, of which 24 cases with fatal outcome were identified during the reporting previous, as described in the previous section.

The top 20 reported PTs were Headache (190), Fatigue (166), Pyrexia (112), Pain in extremity (86), Chills (84), Nausea (83), Dizziness (77), Arthralgia (68), Dyspnoea (68), Myalgia (66), Paraesthesia (66), Malaise (65), Pain (62), Hypoaesthesia (60), Chest pain (41), Asthenia (40), Muscular weakness (39), Influenza like illness (38), Bell's palsy (37), and Pulmonary embolism (37).

16.3.5.3.7 Metastatic Cancer

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and

literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title report title metastatic cancer.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 151 case reports in vaccinees with metastatic cancer who received COVID-19 VACCINE ASTRAZENECA (96.02% spontaneous, 1.32% non-interventional/post-marketing and 2.64% literature).

Of the 151 cases, 53.6% (81) were reported in females, 43.7% (66) in males and gender was not reported in the remaining 2.6% (4) of cases. Age ranged from 18 to <65 years in 43.0% (65(cases; 65+ years in 46.4% (70) reports and age was not reported in the remaining 8.6% (13) of cases. The age group of adult and elderly (age not specified) was reported in 2.0%. The majority of reports 85 (56.3%) were from consumers with the remaining 66 cases (43.7%) being medically confirmed.

Of these 151 cases, 123 (81.5%) were serious due to AE being considered as medially important (75), AE resulted in disability (8), AE required hospitalization (61), AE was life threatening (16), and AE resulted in death (29). Cases may have met more than one criteria for seriousness. The remaining 28 (18.5%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 67.8% (122 events) of the 151 cases, with 24.4% of events occurred within 1 day of vaccination, 24.9% occurred within 2-15 days post-vaccination, 22.8% occurred between 16-200 days post-vaccination, 0.5 % up to 1 year and for 27.3% time to onset was unknown.

Outcome was available for 72.4 % (152 events) of the 151 cases, with 11.9% reported as Recovered, 23.8% as Recovering, 25.8% Not recovered and 4.0% as Recovered with sequelae. Outcome was unknown in 15.2% of reports and was reported as fatal in 29 (19.2%) of the total case count.

Of the 151 reports, there were 29 cases with fatal outcome reported during this period. Age of the 24 vaccinees who died ranged from 54 to 94 years with a median of 72 years. The reported PTs in the 24 cases with a fatal outcome in order of frequency (>3) were: Pulmonary embolism (12), Dyspnoea (11), Fatigue (6), Cough (5), Thrombocytopenia (5), Thrombosis (5), Cerebral infarction (4), Chest pain (4), Death (4), Headache (4), Peripheral swelling (4) and Pneumonia (4). There were 8 cases were a fatal event occurred after 1st dose of vaccine and 6 cases– after 2nd dose. In 6 cases both doses were reported. There was limited information in 9 cases.

The top 20 reported PTs were Pulmonary embolism (28), Thrombocytopenia (24), Headache (22), Dyspnoea (16), Fatigue (13), Arthralgia (9), Deep vein thrombosis (9), Myalgia (9), Pyrexia (9), Thrombosis (9), Chills (8), Cough (8), Nausea (8), Fibrin D dimer increased (7), Metastases to liver (7), Pain in extremity (7), Rash (7), Chest pain (6), COVID-19 (6), Dizziness (6).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 379 cases (97.4% spontaneous, 1.6% non-interventional/post-marketing and 1.1% literature) in individuals with metastatic cancer who received COVID-19 VACCINE ASTRAZENECA.

Of the 379 cases, 57.0% (216 cases) were reported in females, 41.4% (157 cases) in males and gender was not reported in the remaining 1.6% (6) cases. Age ranged from 0 to <18 years in 0.3% (1 case); 18 years to <65 years in 49.1% (186) of the reports and 65+ years in 43.3% (164) cases. The age group of adult and elderly (age not specified) was reported in 1.3% and age was not reported in the remaining 6.1% (23) of cases. The majority of reports 238 (62.8%) were from consumers with the remaining 141 cases (37.2%) being medically confirmed.

Of these 379 cases, 324 (85.5%) were serious due to AE being considered as medially important (220), AE resulted in disability (37), AE required hospitalization (120), AE was life threatening (43), and AE resulted in death (47). Cases may have met more than one criteria for seriousness. The remaining 55 (14.5%) reports were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 77.4% (326 events) of the 379 cases. Most of the events 134 (32.1%) occurred within 1day of vaccination, 102 events (24.2 %) occurred within 2-15 days post-vaccination, 80 events (19.0%) occurred between 16-100 days post-vaccination, 9 events (2.1%) occurred over 1 year after vaccination and for 95 events (22.6%) events time from vaccination to AE onset was unknown.

Outcome was available for 73.6% (450 events), with 19.5% (119 events) reported as Recovered, 22.1% (135 events) as Recovering, 21.1% (129 events) Not recovered, 3.3% (20 events) as Recovered with sequelae and unknown in 26.4% (161 events). The outcome was reported as fatal in 47 (7.7%) of the total case count, of which 29 cases with fatal outcome were identified during the reporting period, as described in the previous section.

The top 20 reported PTs were Headache (78), Pyrexia (60), Fatigue (54), Pulmonary embolism (48), Thrombocytopenia (43), Chills (39), Dyspnoea (34), Nausea (33), Myalgia (26), Arthralgia (23), Deep vein thrombosis (21), Pain (21), Tremor (20), Diarrhoea (19), Malaise (19), Thrombosis (18), Dizziness (17), Asthenia (15), Influenza like illness (15), and Vomiting (15).

16.3.5.3.8 Supplemental Oxygen Use

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title report title Indicators of frailty_oxygen.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 549 case reports in individuals who received COVID-19 VACCINE ASTRAZENECA (97.4% spontaneous, 0.4% non-interventional/post-marketing and 2.0 literature) identified through a Standard Search Query for the report title Indicators of frailty_oxygen.

Of the 549 cases, 62.1% (341) were reported in females, 36.8% (202) in males and gender was not reported in the remaining 1.1% (6 cases). Age ranged from 0 to <18 years in 0.5% (3) cases; 18 to <65 years in 59.0% (324); 65+ years in 17.1% (94) and age was not reported in the remaining 23.0% (126) cases. The age group of adult (age not specified) was reported in 0.4% of cases. The majority of reports (71.6%) were medically confirmed with the remaining 28.4% being consumer reports.

Of these 549 cases, 247 (45%) were serious due to AE being considered as medially important (130), AE resulted in disability (158), AE required hospitalization (35), AE was life threatening (32), and AE resulted in death (38). Cases may have met more than one criteria for seriousness. The remaining 302 (55%) reports were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available for 75.2% (448 events) of the 549 cases, with 48.3% (288 events) occurred within 1 day of vaccination, 12.4% (74 events) occurred within 2-15 days post-vaccination, (79 events) 13.3% occurred between 16-200 days post-vaccination, 1.2% (7 events) up to 1 year and for 24.8% (148 events) time from vaccination to AE onset was unknown.

Outcome was available for 67.2% of the 549 cases, with 29.4% reported as Recovered, 17.6% as Recovering, 13.5% Not recovered, 1.4% as Recovered with sequelae and unknown in 32.8% of reports. The outcome was reported as fatal in 38 (5.3%) of the total case count.

Out of 549 reports, there were 38 cases with fatal outcome reported during this period. Age of the 38 vaccinees who died ranged from 20 to 80 years with a median of 59 years. The reported PTs in the 38 cases with a fatal outcome in order of frequency (>3) were: Dyspnoea (13),

Pulmonary embolism (13), Death (8), Thrombocytopenia (8), Thrombosis (7), Chest pain (6), Fatigue (6), Confusional state (5), Cough (5), Peripheral swelling (5), Asthenia (4), Cerebral infarction (4), Deep vein thrombosis (4), Headache (4), Pneumonia (4). There were 16 cases were a fatal outcome occurred after 1st dose of vaccine and 3 cases – after 2nd dose. In 4 cases both doses were reported. There was limited information in 15 cases.

The top 20 reported PTs were Pyrexia (181), Headache (167), Myalgia (95), Dyspnoea (60), Chills (57), Fatigue (53), Pain (53), Asthenia (47), Nausea (44), Dizziness (39), Arthralgia (33), Vaccination site pain (31), Cough(30), Pulmonary embolism (30), Malaise (29), Vomiting (29), Pain in extremity (27), COVID-19 (24), Diarrhoea (23) and Hypoaesthesia (21).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 1831 cases (97.4% spontaneous, 0.8% non-interventional/post-marketing and 1.4% literature) in individuals identified through a Standard Search Query for the report title Indicators of frailty_oxygen.

Of the 1831 cases, 58.1% (1064) were reported in females, 39.5% (724) in males and gender was not reported in the remaining 2.3% (43) of cases. Age ranged from 0 to <18 years in 0.2% (4) cases; 18 years to <65 years in 60.6% (1109) of the reports and 65+ years in 29.3% (537). The age group of adult and elderly (age not specified) was reported in 0.7% (13) and age was not available for the remaining 9.2% (168) of cases. The majority of cases 1270 (69.4%) were consumers reports with the remaining 30.6% (561) of cases being medically confirmed.

Of these 1831 cases, 1580 (86.3%) were serious due to AE being considered as medially important (1036), AE resulted in disability (207), AE required hospitalization (671), AE was life threatening (221), and AE resulted in death (171). Cases may have met more than one criteria for seriousness. The remaining 251 (13.7%) cases were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 77.9% (1552 events) of the 1831 cases. Most of the events (955) 47.9% occurred within 1day of vaccination, (327) 16.4% occurred within 2-15 days post-vaccination, 12.9% (257) occurred between 16-200 days post-vaccination, 0.7% (13) occurred over 1 year after vaccination and in 22.1% reports time from vaccination to AE onset was unknown.

Outcome was reported in 73.6% (2417 events) of the 1831 cases, with 24.9% (816) reported as Recovered, 21.1% (693) as Recovering, 19.4% (636) Not recovered, 3.1% (101) as Recovered with sequelae and unknown in 26.4% (865) of reports. Outcome was reported as

fatal in 171 (5.2%) of the total case count, of which 38 cases with fatal outcome were identified during the reporting period, as described in previous section.

The top 20 reported PTs were Pyrexia (543), Dyspnoea (523), Headache (447), Oxygen saturation decreased (444), Fatigue (366), Chills (234), Dizziness (229), Nausea (228), Myalgia (203), Pulmonary embolism (158), Malaise (149), Cough (148), Asthenia (145), Chest pain (137), Arthralgia (134), Pain (132), Vomiting (132), Pain in extremity (116), Heart rate increased (98) and Tremor (95).

16.3.5.3.9 Palliative Care

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title Palliative.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 27 case reports in individuals who received COVID-19 VACCINE ASTRAZENECA (97.4% spontaneous, 0.4% non-interventional/post-marketing and 2.0 % literature) identified through a Standard Search Query for the report title Palliative.

Of the 27 cases, 37.0% (10) were reported in females and 63.0% (17) were in males. Age ranged from 18 to <65 years in 18.5% (5) reports; 65+ years in 77.8% (21) and age was not reported in the remaining 3.7% (1) of cases. The majority of reports 14 (51.9%) were medically confirmed with the remaining 13 (48.1%) being consumer reports.

All of these 27 cases, were serious due to AE being considered as medially important (17), AE resulted in disability (4), AE required hospitalization (16), AE was life threatening (3), and AE resulted in death (17). Cases may have met more than one criteria for seriousness.

Information on time to onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available in 79.3% (23 events), of which 20.7% (6 events) occurred within 1 day of vaccination, 24.1% (7 events) occurred within 2-15 days post-vaccination, 31.0% (9 events) occurred between 16-200 days post-vaccination, (1 event) 3.4% up to 1 year and in 20.7% (6 events) time from vaccination to AE onset was unknown.

Outcome was reported for 69.4% (34 events) of the 27 cases, with 6.1% (3 events) reported as Recovered, 4.1% (2 events) as Recovering, 24.5% (12 events) Not recovered and unknown for 30.6% (15 events). Outcome was reported as fatal for 17 (34.7%) of the total case count.

Out of 27 reports, there were 17 cases with fatal outcome reported during this period. Age of the 17 vaccinees who died ranged from 53 to 93 years with a median of 77 years. The reported PTs in the 17 cases with fatal outcome in order of frequency (>2) were: Cerebrovascular accident (5), Thrombosis (3), Abdominal distension (2), Abnormal weight gain (2), Ascites (2), Dyspnoea (2), Electrolyte imbalance (2), Encephalopathy (2), Facial paralysis (2), Hepatic cirrhosis (2), Hypotension (2), Mesenteric artery thrombosis (2), Oedema peripheral (2), Platelet count decreased (2), Pneumonia (2), Sarcopenia (2), Thrombocytopenia (2), Varices oesophageal (2). There were 7 cases were a fatal outcome occurred after 1st dose of vaccine and 3 cases – after 2nd dose. In 1 case both doses were reported. There was limited information in 6 cases.

The top 20 reported PTs were Cerebrovascular accident (5), Dyspnoea (5), Malaise (5), Pulmonary embolism (4), Thrombocytopenia (4), Fibrin D dimer increased (3), Headache (3), Pneumonia (3),Thrombosis (3), Cardiac failure (2), Circulatory collapse (2), Confusional state (2), Depressed level of consciousness (2), Facial paralysis (2), Hypotension (2), Platelet count decreased (2), Urinary tract infection (2), Vomiting (2), Abdominal discomfort (1), and Abdominal distension (1).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 98 cases (96.9% spontaneous s, Non-interventional / Post-marketing1.0%, and literature 2.0%) in individuals identified through Standard Search Query for the report title Palliative.

Of the 98 cases, 45.9% (45) were reported in females and 54.1% (53) were in males. Age ranged from 18 years to <65 years in 22.4% (22) cases; 65+ years in 72.4% (71) and age was not reported for the remaining 5.1% (5) cases. The majority of cases 57 (58.2%) were medically confirmed with the remaining 41 (41.8%) being consumer reports.

Of these 98 cases, 95 (96.9%) were serious due to AE being considered as medially important (57), AE resulted in disability (18), AE required hospitalization (41), AE was life threatening (22), a AE resulted in death (52). Cases may have met more than one criteria for seriousness. The remaining 3 (3.1%) cases were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 78.8% (82 events) of the 98 cases. Most of the events 31.7% (33) occurred within 1 day of vaccination, 25.0% (26) occurred within 2-15 days post-vaccination, 19.2% (20) occurred between 16-200 days post-vaccination, 2.9% (3) occurred over 1 year after vaccination and in 21.2% (22 events) time from vaccination to AE onset was unknown.

Outcome was reported for 71.7% (119 events) of the 98 cases, with 10.8% reported as Recovered, 4.8% as Recovering, 23.5% Not recovered, 1.2% as Recovered with sequelae and unknown in 28.3% of reports. Outcome was reported as fatal in 52 (31.3%) of the total case count, of which 17 cases with fatal outcome where identified during the reporting period, as described in the previous section.

The top 20 reported PTs were Cerebrovascular accident (13), Malaise (13), Death (12), Dyspnoea (10), Headache (10), Thrombocytopenia (8), Vomiting (7), Cerebral haemorrhage (6), Confusional state (6), Facial paralysis (6), Fatigue (6), Nausea (6), Pulmonary embolism (6), Syncope (6), Myalgia (5), Pain in extremity (5), Pyrexia (5), Chills (4), Decreased appetite (4) and Depressed level of consciousness (4).

16.3.5.3.10 Pressure Ulcers

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified through a Standard Search Query for the report title _Pressure ulcers.

Interval Review (29 June 2021 – 28 December 2021)

The search identified a total of 1003 case reports (93.9% spontaneous, 5.1% non-interventional/post-marketing and 1.0% literature) in individuals with underlying pressure ulcers who received COVID-19 VACCINE ASTRAZENECA.

Of the 1003 cases, 69.0% (692) were reported in females, 29.5% (296) in males and gender was unknown in 1.5% (15) of cases. Age ranged from 0 to <18 years in 0.1% (1); 18 to <65 years in 71.3% (715); 65+ years in 21.4% 215). Age was not reported for the remaining 6.6% (66) of cases. The majority of reports 782 (78.0%) were from consumers with the remaining 221 (22%) cases being medically confirmed.

Of these 1003 cases, 490 (48.9%) were serious due to AE being considered as medially important (346), AE resulted in disability (92), AE required hospitalization (147), AE was life threatening (34), and AE resulted in death (22). Cases may have met more than one criteria for seriousness. The remaining 513 (51.1%) cases were non serious.

Information on time to AE onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available in 68.8% (811 events) of the 1003 cases, of which 35.6% (420) of events occurred within 1 day of vaccination, 19.6% (473) occurred within 2-15 days post-vaccination, 12.6% (148) occurred between 16-200 days post-vaccination, 1.0% (12) up to 1 year and for the remaining 31.2% cases time from vaccination to AE onset was unknown.

Outcome was available for 82.7% (1287) of the 1003 cases, with 27.4% (427) reported as Recovered, 18.8% (293) as Recovering, 32.2% (502) Not recovered and unknown in 17.3% (270) of reports. Outcome was reported as fatal in 22 (1.4%) of the total case count.

Out of 1003 cases, there were 22 reports with fatal outcome reported during this period. Age of the 22 vaccinees who died ranged from 20 to 90 years with a median of 69.5 years. The reported PTs in the 22 cases with a fatal outcome in order of frequency (>2) were: Pulmonary embolism (9), Thrombocytopenia (8), Death (6), Cerebrovascular accident (4), Deep vein thrombosis (4), Dysarthria (4), C-reactive protein increased (3), Decubitus ulcer (3), Diarrhoea (3), Hypotension (3), Inflammatory marker increased (3), Multiple organ dysfunction syndrome (3), Pain in extremity (3), Peripheral swelling (3), Thrombosis (3) and Vaccination error (3). There were 10 cases were a fatal outcome occurred after 1st dose of vaccine and 2 cases after 2nd dose. In 5 cases both doses were reported. There was limited information in 5 cases.

The top 20 reported PTs were Headache (267), Pyrexia (201), Mouth ulceration (188), Fatigue (187), Chills (118), Arthralgia (117), Myalgia (106), Aphthous ulcer (98), Nausea (96), Pain in extremity (94), Malaise (87), Dizziness (85), Pain (67), Colitis ulcerative (62), Diarrhoea (60), Asthenia (46), Influenza like illness (42), Paraesthesia (41), Vomiting (41) and Abdominal pain (40).

Cumulative Review (29 December 2020 – 28 December 2021)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 3622 cases (96.7% spontaneous, 2.9% non-interventional/post-marketing, 0.3% literature and 0.02% each from the study D8110C00001 and ICMR/SII-AZD-COVID-19/2020) in individuals with pressure ulcers.

Of the 3622 cases, 70.8% (2566) were reported in females, 26.7% (966) in males and gender was not reported in the remaining 2.5% (90) of cases. Age ranged from 0 to <18 years in 0.2% (6); 18 years to <65 years in 74.1% (2684) of the reports and 65+ years in 17.8% (644) cases. The age group of adult and elderly (age not specified) was reported for 0.7% cases. Age was not reported in the remaining 7.3% (264) of cases. The majority of reports 3019 (83.4%) were from consumers with the remaining 603 (16.6%) cases being medically confirmed.

Of these 3622 cases, 2159 (59.6%) were serious due to AE being considered as medially important (1773), AE resulted in disability (300), AE required hospitalization (315), AE was life threatening (84), and AE resulted in death (50). Cases may have met more than one criteria for seriousness. The remaining 1463 (40.4%) cases were non serious.

Information on time to AE onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available for 80.0% (3059 events) of the 3622 cases. Most of the

events 52.4% (2004) occurred within 1 day of vaccination, 20.1% (769) occurred within 2-15 days post-vaccination, 7.0% (266) occurred between 16-200 days post-vaccination, 0.5% (20) occurred over 1 year after vaccination and for 20.0% (769) reports time from vaccination to AE onset was unknown.

Outcome was available for 82.9% (3474) of the 3622 cases, with 27.1% reported as Recovered, 22% as Recovering, 30.0% Not recovered, 2.6% as Recovered with sequelae. and unknown in 17% (1089) of reports. Outcome was reported as fatal in 50 (0.8%) of the total case count, out of which 22 cases with fatal outcome were identified during the reporting period, as described in the previous section.

The top 20 reported PTs were Headache (1,179), Pyrexia (930), Mouth ulceration (919), Fatigue (839), Chills (616), Nausea (489), Myalgia (479), Arthralgia (402), Dizziness (332), Pain in extremity (325), Malaise (273), Aphthous ulcer (270), Diarrhoea (213), Pain (213), Vomiting (175), Oropharyngeal pain (168), Influenza like illness (165), Colitis ulcerative (153), Pruritus (139) and Paraesthesia (136).

Summary

This review presented the cumulative and periodic data in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail for the following categories.

- **Frailty:** Cumulatively 659 cases were identified, out of which majority (78.15%) were reported in females. Out of 659 cumulative reports, 30 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (59.0%). Of these 659 cases, 88 (7.5%) cases reported fatal outcome, of which 14 cases with fatal outcome were reported during the interval period.

- **Hip Fracture:** Cumulatively 23 cases were reported, out of which majority (78.3%) were reported in females. 5 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (69.6%). No fatal cases were reported for this category during the interval period.

- **Cachexia:** Cumulatively 180 cases were reported, out of which majority (58.3%) were reported in females. 101 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (64.4%)). Of these 180 cases, there were 4 cases with fatal outcome reported during this period.

- **Bladder Incontinence:** Cumulatively 4085 cases, cases were reported, out of which majority (67.9%) were reported in females. 1399 cases were reported in the reporting

interval. Majority of the cases in the cumulative period were serious (72.5%) Of these 4085 cases, there were 67 cases with fatal outcome reported during this period.

- **Dementia:** Cumulatively 2327 cases, cases were reported, out of which majority (65.3%) were reported in females. 951 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (76.5%). Of these 2327 cases, there were 53 cases with fatal outcome reported during this period.

- **Long term Frailty:** Cumulatively 675 cases, were reported, out of which majority (63.3%) were reported in females. 316 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (92.7%). Of these 675 cases, there were 24 cases with fatal outcome reported during this period.

- **Metastatic Cancer:** Cumulatively 379 cases, were reported, out of which majority (57.0%) were reported in females. 151 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious ((85.5%)). Of these 379 cases, there were 29 cases with fatal outcome reported during this period.

- **Supplemental Oxygen Use:** Cumulatively 1831 cases, cases were reported, out of which majority (58.1%) were reported in females. 549 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (86.3%). Of these 1831 cases, there were 38 cases with fatal outcome in the reporting interval.

- **Palliative Care:** Cumulatively 98 cases were reported, out of which majority (and 54.1%) were reported in males. 27 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (96.9%) Of these 98 cases, there were 17 fatal cases reported during interval period

- **Pressure Ulcers:** Cumulatively the 3622 cases, cases were reported, out of which majority (70.8%) were reported in females. 1003 cases were reported in the reporting interval. Majority of the cases in the cumulative period were serious (59.6%). Of these 3622 cases, there were 22 fatal cases reported during interval period.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders.

Conclusion

This cumulative and periodic review of available data from the use of COVID-19 VACCINE ASTRAZENECA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to AZD1222. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.3.

16.3.5.4 Use of COVID-19 VACCINE ASTRAZENECA with other vaccines / Interactions with other vaccines

The safety, immunogenicity, and efficacy of COVID-19 VACCINE ASTRAZENECA when co-administered with other vaccines (either interchangeably with alternative licensed COVID-19 vaccines, or concurrently with seasonal illness vaccines) has not been evaluated in clinical trials. Therefore, while there is currently no evidence to suggest the safety profile of the subjects receiving COVID-19 VACCINE ASTRAZENECA when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

A cumulative search of the AstraZeneca Global Safety Database through was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA with other vaccines, including seasonal influenza vaccine and pneumococcal pneumonia vaccine. Reports were identified in the Global Safety Database through a search of the concomitant medications for: seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine.

Influenza Vaccine

Assessment for cases received with Influenza Vaccine (reporting interval):

This search identified a total of 2141 cases (66.9% spontaneous cases, 32.7% non-interventional/post-marketing cases, 0.1% Clinical trial, and 0.3% literature) for the topic use of COVID-19 VACCINE ASTRAZENECA with seasonal influenza vaccine.

Of the 2141 cases, 68.8% (1474) were reported in females, 29.1% (622) - in males and gender was not reported in the remaining 2.1% (45) of cases. The age ranged from 18 years to <65 years in 53.9% (1153) of the reports, 65+ years in 40.4% (864), and 0.4% (8) in less than 18 years of age. In 5.2% (112) cases the age was reported as unknown. Of the 2141 reports, 7.5% (161) were medically confirmed, with remaining 92.5% (1980) being consumer reports.

Of the 2141 reports, 33.7% (721) were serious due to the AE being considered as medially important (641), the AE resulted in disability (87), AE required hospitalization (122), AE was life threatening (42), and the AE resulted in death (21). Cases may have met more than one criteria for seriousness. The remaining 66.3% (1420) cases were non-serious.

A total of 6832 AEs were reported within the 2141 reports.

The time to onset from vaccination to the event was available for 10557 AEs of which 17.6% of events occurred within day 0 of vaccination, 16.4% occurred on day 1 post vaccination, 8.9% events occurred within days 2-15 post-vaccination, 15.9% events occurred between 16-200 days post-vaccination, 7.7% events occurred > 200 days post-vaccination, and for 33.4% events the time from vaccination to AE onset was not reported.

Outcome was reported for 43.9% (6959), with 46.6% reported as recovered, 16.0% as recovering, 1.1% as recovering with sequelae, 21.2% not recovered, and 0.8% as fatal and 14.3% as unknown. The top 20 reported PTs were headache (714), fatigue (530), pyrexia (348), pain in extremity (326), chills (308), myalgia (250), arthralgia (212), nausea (208), pain (132), dizziness (112), malaise (99), influenza like illness (93), pruritus (77), injection site pain (69), rash (65), diarrhoea (64), asthenia (60), feeling cold (59), paraesthesia (57), and vomiting (53).

Assessment for cases received with Influenza Vaccine (cumulative search):

This search identified a total of 12592 cases (86.8% spontaneous cases, 13.1% non-interventional/post-marketing cases, 0.01% Clinical trial, and 0.07% literature) for the topic use of COVID-19 VACCINE ASTRAZENECA with seasonal influenza vaccine.

Of the 12592 cases, 74.0% (9322) were reported in females, 23.5% (2960) in males and gender was not reported in the remaining 2.5% (310) of cases. The age ranged from 18 years to <65 years in 67.4% (8492) of the reports, 65+ years in 27.0% (3398), and 0.36% (45) in less than 18 years of age. In 5.2% (657) cases the age was reported as unknown. Of the 12592 reports, 7.7% (972) were medically confirmed, with remaining 92.3% (11620) being consumer reports.

Of the 12592 reports, 63.9% (8046) were serious due to the AE being considered as medially important (7438), the AE resulted in disability (679), AE required hospitalization (364), AE was life threatening (133), and the AE resulted in death (53). Cases may have met more than one criteria for seriousness. The remaining 36.1% (4546) cases were non-serious.

A total of 51364 AEs were reported within the 12592 cases received.

The time to onset from vaccination to the event was available for 57749 events of which 32.1% occurred the same day as vaccination, 24.8% occurred on day 1 post-vaccination, 9.1%

events occurred within days 2-15 post-vaccination, 4.2% events occurred between 16-200 days post-vaccination, 1.8% events occurred > 200 days post-vaccination, and for 28.0% events the time from vaccination to AE onset was not reported.

Outcome was reported for 53280 events, with 42.2% reported as recovered, 20.5% as recovering, 1.3% as recovering with sequelae, 21.7% not recovered, 0.2% as fatal, and 14.1% as unknown. The top 20 reported PTs were headache (5707), fatigue (3801), pyrexia (3677), chills (3339), nausea (2412), myalgia (2048), arthralgia (1589), pain in extremity (1456), dizziness (1250), pain (977), malaise (884), influenza like illness (764), tremor (732), vomiting (668), hyperhidrosis (553), Diarrhoea (530), decreased appetite (493), influenza (455), migraine (443) and paraesthesia (441).

Herpes Vaccine

Assessment for cases received with Herpes vaccine (Reporting Interval):

No cases were reported with Herpes vaccine in the reporting interval.

Assessment for cases received with Herpes vaccine (Cumulative search):

This search identified 1 spontaneous case received from a pharmacist via Health Authority for the topic use of COVID-19 VACCINE ASTRAZENECA with Herpes vaccine. This case was serious due to hospitalisation and was reported in a PPD years PPD , with a medical history of PPD , who experienced the events Thrombocytopenia(TCP), Pulmonary embolism (PE), COVID-19 pneumonia, sickle cell anaemia with crisis, chest pain, lung opacity, atelectasis, and oxygen saturation decreased.

The time to onset from vaccination to the events was reported to be 17 days for sickle cell crisis, 22 days for PE and oxygen saturation decreased. The time to onset from vaccination to the other events was unknown.

The outcome for the events TCP, PE, COVID-19 pneumonia, sickle cell anaemia with crisis, and oxygen saturation decreased was reported as recovered. The outcome for the events chest pain, lung opacity, and atelectasis was unknown.

Pneumococcal Vaccine

Assessment for cases received with Pneumococcal vaccine (Reporting interval):

This search identified a total of 77 cases (85.7% spontaneous cases, 13.0% non-interventional/post-marketing cases, and 1.3% literature cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Pneumococcal vaccine.

Of the 77 cases, 67.5% (52) were reported in females, and 32.5% (25) - in males. The age ranged from 18 years to <65 years in 35.1% (27) of the reports, 65+ years in 51.9% (40), and 1.3% (1) in less than 18 years of age. In 11.7% (9) cases the age was not reported. Of the 77 reports, 27.3% (21) cases were medically confirmed with remaining 72.7% (56) being consumer reports.

Of the 77 reports, 45.5% (35) were serious due to the AE being considered as medially important (29), the AE resulted in disability (5), AE required hospitalization (5), AE was life threatening (3) Cases may have met more than one criteria for seriousness. The remaining 54.5% (42) cases were non-serious.

A total of 310 AEs were reported within the 77 reports.

The time to onset from vaccination to the event was available 485 events of which 15.5% occurred within day 0 of vaccination, 13.0% occurred on day 1 post vaccination, 6.2% events occurred within days 2-15 post-vaccination, 19.8% events occurred between 16-200 days post-vaccination, 8.5% events occurred > 200 days post-vaccination. For 37.1% events the time to onset post vaccination was not reported.

Outcome was reported for 313 events , with 36.4% reported as recovered, 10.9% as recovering, 1.9% as recovering with sequelae, 28.4% not recovered and 22.4% as unknown. The top 20 reported PTs were headache (20), fatigue (19), myalgia (15), pain in extremity (11), chills (10), arthralgia (8), nausea (7), pain (7), dizziness (6), pyrexia (6), rash (5), condition aggravated (4), limb discomfort (4), malaise (4), asthenia (3), decreased appetite (3), Guillain-Barre syndrome (3), heart rate increased (3), influenza like illness (3), and injection site pain (3).

Assessment for cases received with Pneumococcal vaccine (Cumulative search):

This search identified a total of 292 cases (87.3% spontaneous cases, and 12.3% non-interventional/post-marketing cases, and 0.4% literature cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Pneumococcal vaccine.

Of the 292 cases, 70.9% (207) were reported in females, 27.1% (79) - in males and gender was not reported in the remaining 2.1% (6) of cases. The age ranged from 18 years to <65 years in 47.3% (138) of the reports, 65+ years in 45.9% (134), and 0.7% (2) in less than 18 years of age. In 5.5% (16) cases the age was not reported. Of the 292 reports,16.1% (47) cases were medically confirmed with remaining 83.9% (245) being consumer reports.

Of the 292 reports, 63.7% (186) were serious due to the AE being considered as medially important (164), the AE resulted in disability (19), AE required hospitalization (15), and AE

was life threatening (5). Cases may have met more than one criteria for seriousness. The remaining 36.3% (106) cases were non-serious.

A total of 1351 AEs were reported within the 292 reports.

The time to onset from vaccination to the event was available for 1570 events of which, 31.3% occurred within day 0 of vaccination, 18.4% occurred on day 1 post vaccination, 7.3% events occurred within days 2-15 post-vaccination, 6.9% events occurred between 16-200 days post-vaccination, 2.6% events occurred > 200 days post-vaccination. For 33.5% events the time to AE onset post vaccination was not reported.

Outcome was reported for 1382 events, with 42.8% reported as recovered, 15.8% as recovering, 1.4% as recovering with sequelae, 21.9% not recovered and 17.9% as unknown. The top 20 reported PTs were headache (118), fatigue (87), pyrexia (72), , chills (72), nausea (53), myalgia (53), pain in extremity (42), arthralgia (36), dizziness (35), malaise (25), pain (22), tremor (20), influenza like illness (17), asthenia (15),feeling cold (15), decreased appetite (12), hyperhidrosis (12), oropharyngeal pain (11), vomiting (11), and paraesthesia (10).

Varicella Vaccine

Assessment for cases received with Varicella vaccine (Reporting interval):

This search identified a total of 20 cases (80.0% spontaneous cases, and 20.0% non-interventional/post-marketing cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Varicella vaccine.

Of the 20 cases, 50.0% (10) were reported in females and 50.0% (10) - in males. The age ranged from 18 years to <65 years in 25.0% (5) of the reports, and 65+ years in 75.0% (15). Of the 20 reports, 35.0% (7) cases were medically confirmed with remaining 65.0% (13) being consumer reports.

Of the 20 reports, 45.0% (9) were serious due to the AE being considered as medially important (7), the AE resulted in disability (1), AE required hospitalization (2), and AE was life threatening (2). Cases may have met more than one criteria for seriousness. The remaining 55.0% (11) cases were non-serious.

A total of 65 AEs were reported within the 20 reports.

The time to onset from vaccination to the was available for 107 events of which , 7.5% occurred within day 0 of vaccination, 8.4% occurred on day 1 post vaccination, 2.8% events occurred within days 2-15 post-vaccination, 29.0% events occurred between 16-200 days post-vaccination and 15% events occurred >200 days post-vaccination. For 37.4% events the time to onset post vaccination was not reported.

Outcome was reported for 65 events, with 23.1% reported as recovered, 15.4% as recovering, 18.5% as not recovered, and 43.1% as unknown. The top 20 reported PTs were herpes zoster (5), headache (4), pyrexia (4), rash (4), vaccination failure (4), chills (3), pain in extremity (3), pruritus (3), blister (2), inappropriate schedule of product administration (2), oropharyngeal pain (2), pain (2), acute myocardial infarction (1), application site pain (1), asthenia (1), chest discomfort (1), cough (1), deep vein thrombosis (1), diplopia (1), dizziness (1).

Assessment for cases received with Varicella vaccine (Cumulative search):

This search identified a total of 47 cases (87.2% spontaneous cases, and 12.8% non-interventional/post-marketing cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Varicella vaccine.

Of the 47 cases, 59.6% (28) were reported in females 36.2% (17) in males and gender was not reported in the remaining 4.3% (2) of cases. The age ranged from 18 years to < 65 years in 23.4% (11) of the reports, and 65+ years in 72.3% (34). In 4.3% (2) cases the age was not reported. Of the 47 reports, 25.5% (12) were medically confirmed with remaining 74.5% (35) being consumer reports.

Of the 47 reports, 53.2% (25) were serious due to the AE being considered as medially important (23), the AE resulted in disability (2), AE required hospitalization (2), and AE was life threatening (2). Cases may have met more than one criteria for seriousness. The remaining 46.8% (22) cases were non-serious.

A total of 178 AEs were reported within the 47 reports.

Time to onset from vaccination to the event was available for 232 events reported of which 16.4% of events occurred within day 0 of vaccination, 12.9% occurred on day 1 post vaccination, 6.5% events occurred within days 2-15 post-vaccination, 15.1% events occurred between 16-200 days post-vaccination and 6.9% events occurred > 200 days post-vaccination. 42.2% events where the number of days to onset post vaccination was not reported.

Outcome was reported for 180 events, with 30.6% reported as recovered, 20.6% as recovering, 2.8% as recovered with sequelae, 18.3% not recovered, and 27.8% as unknown. The top 20 reported PTs were pyrexia (13), headache (11), chills (8), fatigue (8), herpes zoster (7), nausea (7), pain in extremity (5), arthralgia (4), myalgia (4), rash (4), vaccination failure (4), blister (3), pain (3), pruritus (3), abdominal pain upper (2), deep vein thrombosis (2), dizziness (2), heart rate increased (2), inappropriate schedule of product administration (2), and influenza like illness (2).

Conclusion

This cumulative and periodic review of the Use of COVID-19 VACCINE ASTRAZENECA with other vaccines/Interactions with other vaccines did not indicate any safety concerns.

From the data identified cumulatively and during the reporting period Use of COVID-19 VACCINE ASTRAZENECA with other vaccines/Interactions with other vaccines will continue to be considered missing information for COVID-19 VACCINE ASTRAZENECA.

Use of COVID-19 VACCINE ASTRAZENECA with other vaccines/Interactions with other vaccines will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to AZD1222. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.4.

16.4 Characterisation of risks

At the end of the reporting period, the COVID-19 VACCINE ASTRAZENECA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 5.0, dated 09 December 2021) included the following important identified and important potential risks, and missing information (see Table 158). Characterisations of the safety concerns are presented in Sections 16.4.1, 16.4.2 and 16.4.3 respectively.

Table 158 Summary of safety concerns – AstraZeneca Core Risk Management Plan for COVID-19 VACCINE ASTRAZENECA (Version no. 5.0, dated 09 December 2021)

Risk Category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Immune-mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)
	Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia
Missing information	Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women
	Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency
	Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease
	Use of COVID-19 VACCINE ASTRAZENECA with other vaccines

CVST, Cerebrovascular venous sinus thrombosis; VAED, Vaccine-associated enhanced disease.

In the following sections, detailed information is given on the important identified and potential risks, and missing information included in Table 158 above.

16.4.1 Important identified risks

The following safety concerns are considered as Important identified risks:

- Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia (Section 16.4.1.1).

16.4.1.1 Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Table 159 Important identified risk – Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Characterisation	Summary
Frequency	There were no reports of thrombosis concurrent with thrombocytopenia in the clinical development programme. Very rare events of serious thrombosis concurrent with thrombocytopenia (including fatal events), have been observed following vaccination with COVID-19 VACCINE ASTRAZENECA during post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.
Potential mechanism	The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with AZD1222 is unknown. Several hypothetical biologic mechanisms (eg, vaccine induction of PF4 autoantibodies) have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021 (NEJM)); however, none of these hypotheses have been confirmed.
Risk groups or risk factors	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.
Preventability	Prevention of thrombosis concurrent with thrombocytopenia in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the CDS, healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed toseek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal

Table 159 Important identified risk – Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Characterisation	Summary
	pain, or unusual skin bruising and/or petechia a few days after vaccination.
Impact on the risk-benefit balance of the product	Thrombosis with thrombocytopenia is a potentially life-threatening event if not recognised ormanaged appropriately, may result in persistent or significant disability or incapacity. Thrombosis with thrombocytopenia requires immediate medical intervention.
Public health impact	The public health benefit of vaccination is considered to outweigh the very rare occurrence ofthese events.

CDS Core Data Sheet, PF4 Platelet Factor 4.

16.4.2 Important potential risks

The following 3 safety concerns are considered as important potential risks:

- Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions (Section 16.4.2.1).
- Vaccine-associated enhanced disease (VAED)/Vaccine-associated enhanced respiratory disease (Section 16.4.2.2).
- Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia (Section 16.4.2.3).

16.4.2.1 Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Table 160 Important potential risk – Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Characterisation	Summary
Frequency	Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the US study, neurologic or neuroinflammatory AESIs were reported in 0.6% (121/21,587 participants) in the AZD1222 group and 0.4% (48/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, neurologic or neuroinflammatory AESIs were reported in 0.7% (81/12,282 participants) in the AZD1222 group and 0.8% (90/11,963 participants) in the control group. Furthermore, in the pooled Oxford studies no clinically meaningful imbalance was noted in the incidence of AESIs of neuroinflammatory disorders, which were reported in 7

Table 160 Important potential risk – Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Characterisation	Summary
	participants(0.1%) in the AZD1222 group and 4 participants (<0.1%) in the control group in the pooled safety dataset (any dose group). Of these, the most frequently reported events were non-serious AEs of facial paralysis occurred in 4 participants in the AZD1222 group and 3 participants in the control group. In the US study, there were 5 non-serious AEs of facial paralysis, all in the AZD1222 group. In the US study, there was 1 SAE of a demyelinating event: a participant in the AZD1222 group had an AE initially reported as Guillain-Barre syndrome, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. In the pooled Oxford studies, there were 3 SAEs of demyelinating events: 2 cases in the AZD1222 group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group.
Potential mechanism	Several hypothetical biologic mechanisms have been proposed to explain the pathophysiologyof neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton et al 1994).
Risk groups or risk factors	There are no known risk factors for the development of immune-mediated neurologicalconditions following vaccination.
Preventability	Prevention of immune-mediated neurological conditions in the context of SARS-COV-2 vaccination is unknown.
Impact on the risk-benefit balance of the product	Severe immune-mediated neurological conditions, if not recognised or managed appropriately,may result in persistent or significant disability or incapacity.
Public health impact	Immune-mediated neurological disorders are very rare, and as such the public health benefitof vaccination is considered to outweigh the very rare potential occurrences of such events.

AE Adverse Event, AESI Adverse Event of Special Interest, SAE Serious Adverse Events, SARS-COV-2 Severe Acute Respiratory Syndrome Coronavirus 2, US United States.

16.4.2.2 Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease

Table 161 Important potential risk – Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease

Characterisation	Summary
Frequency	In the AZD1222 clinical programme, there was no evidence of an association between AZD1222 and VAED; proportionally more AESIs based on study specific lists of terms related to COVID-19 occurred in the control group than among AZD1222 recipients. In theUS study, COVID-related AESIs were reported in 1.7% (374/21,587 participants) in the AZD1222 group and 3.4% (362/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, COVID-related AESIs were reported in 0.1% (15/12,282 participants) in the AZD1222 group and 0.3% (36/11,963 participants) in the control group. There have been no confirmed post-marketing reports of VAED/VAERD.
Potential mechanism	The pathogenesis of VAED/VAERD in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from nonclinical studies (Haynes et al 2020).
Risk groups or risk factors	There are no known risk factors identified for VAED/VAERD.
Preventability	Prevention of VAED/VAERD in the context of SARS-COV-2 is currently unknown.
Impact on the risk-benefit balance of the product	Vaccine-associated enhanced disease may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED/VAERD may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation; and patients diagnosed with acute respiratory distress syndrome (ARDS) have poorer prognosis and potentially higher mortality rate.
Public health impact	As this safety concern is currently theoretical in relation to COVID-19 VACCINE ASTRAZENECA administration, there is no public health impact noted at this time.

AESI Adverse Event of Special Interest; ARDS Acute Respiratory Distress Syndrome, SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2, VAED/ VAERD Vaccine-Associated Enhanced Disease/ Vaccine-Associated Enhanced Respiratory Disease.

16.4.2.3 Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia

Table 162 Important potential risk – Cerebrovascular venous sinus thrombosis (CVST)

Characterisation	Summary
Frequency	There were no reports of CVST identified in the AZD1222 group in the US study (D8110C00001 [DCO: 15 March 2021] and D8111C00002 [DCO: 10 January 2021]) and in the pooled Oxford studies (COV001, COV002, COV003 and COV005; DCO: 07 December 2020). In the post-marketing setting, CVST without thrombocytopenia have been reported very rarely following vaccination with COVID-19 Vaccine AstraZeneca.
Potential mechanism	The exact mechanism of CVST without thrombocytopenia following administration with COVID-19 VACCINE ASTRAZENECA is unknown.
Risk groups or risk factors	There are no known risk factors for the development of CVST without thrombocytopenia following vaccination.
Preventability	Prevention of CVST without thrombocytopenia in the context of COVID-19 vaccination is currently unknown. The events of CVST without thrombocytopenia can be fatal and may require different treatment approaches than thrombosis in combination with thrombocytopenia.
Impact on the risk-benefit balance of the product	CVST without thrombocytopenia is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.
Public health impact	The public health benefits of vaccination are considered to outweigh the very rare occurrence of these events.

CVST Cerebral Venous Sinus Thrombosis, DCO Data Cut-Off, US United States.

16.4.3 Missing information

The following 4 safety concerns are considered as missing information:

- Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding (Section 16.4.3.1)
- Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency / Use in immunocompromised patients (Section 16.4.3.2)
- Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease / Use in frail patients with co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Section 16.4.3.3)
- Use of COVID-19 VACCINE ASTRAZENECA with other vaccines / Interactions with other vaccines (Section 16.4.3.4)

16.4.3.1 Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding

There is a limited amount of data received cumulatively and during the reporting period from the use of COVID-19 VACCINE ASTRAZENECA in pregnant and/or lactating women, or from women who became pregnant after receiving COVID-19 VACCINE ASTRAZENECA.

Use of COVID-19 VACCINE ASTRAZENECA during pregnancy and neonatal outcome is considered as AESI for COVID-19 VACCINE ASTRAZENECA and reviews of these topics have been provided in each COVID-19 VACCINE ASTRAZENECA Summary Safety Report (SSR) with the last SSR submitted globally for the period up to 30 November 2021. In addition, review and analysis of the cumulative and periodic data for the pregnancy and neonatal outcomes topics is included in Section 16.3.5.1 of this PBRER. To date, from the data reviewed and analysed during the monthly intervals, during the current reporting period and also from the cumulative experience, no unexpected trends or safety concerns were identified and no causal relationship between adverse pregnancy outcomes or negative effects on neonates has been established.

Pregnancy and neonatal outcomes will continue to be kept under close surveillance by AstraZeneca and will report any relevant new information in subsequent Periodic Safety Update Reports . In addition, use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women will be investigated in the planned PASS activities (EAS, a post-marketing observational study using existing secondary health data sources and a pregnancy registry).

16.4.3.2 Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency / Use in immunocompromised patients

Vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response; however immunocompromised individuals may also be at greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability.

Although there is no evidence that the safety profile of this population receiving COVID-19 VACCINE ASTRAZENECA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Review of the available cumulative and periodic data from the use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency and in immunocompromised patients did not identify any particular safety concerns. The adverse events observed post vaccination in patients with autoimmune and/or inflammatory disorders appear to be similar to those in general population.

Use of COVID-19 VACCINE ASTRAZENECA in patients with autoimmune and/or inflammatory disorders will continue to be considered as Missing Information in the EU Risk Management Plan and updates on this topic will be provided in subsequent Periodic Safety Update Reports.

In addition, use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency will be investigated in the planned PASS activities (EAS and a post-marketing observational study using existing secondary health data sources, a post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency, and an interventional study in immunocompromised subjects) and in ongoing clinical study COV005.

16.4.3.3 Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease / Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Subjects with severe and/or uncontrolled underlying disease are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of COVID-19 VACCINE ASTRAZENECA in this population will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Current review of the available cumulative and periodic data from the use of COVID-19 VACCINE ASTRAZENECA in subjects with frailty, severe and/or uncontrolled diseases did not identify any particular safety concerns.

This topic will continue to be considered as Missing Information and will be kept under close surveillance by AstraZeneca. Any relevant new information will be reported in subsequent Periodic Safety Update Reports.

In addition, use of COVID-19 VACCINE ASTRAZENECA in patients with severe and/or uncontrolled diseases will be investigated in the planned PASS activities (EAS and a post-marketing observational study using existing secondary health data sources).

16.4.3.4 Use of COVID-19 VACCINE ASTRAZENECA with other vaccines / Interactions with other vaccines

The safety, immunogenicity, and efficacy of COVID-19 VACCINE ASTRAZENECA when co-administered with other vaccines (ie, concurrently with seasonal illness vaccines) has not been evaluated. Therefore, while there is currently no evidence to suggest the safety profile of the subjects receiving COVID-19 VACCINE ASTRAZENECA when co-administered with

other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

No new safety concerns have been identified following analysis of available cumulative and periodic data from the use of COVID-19 VACCINE ASTRAZENECA with other vaccines/Interactions with other vaccines. This topic will continue to be considered missing information for COVID-19 VACCINE ASTRAZENECA and updates will be provided in subsequent Periodic Safety Update Reports.

In addition, the co-administration of COVID-19 VACCINE ASTRAZENECA with other vaccines (either together, or 30 days before or after administration) will be investigated in the planned PASS activities (EAS studies and a post-marketing observational study using existing secondary health data sources).

16.5 Effectiveness of risk minimisation

No information on the effectiveness of risk minimisation activities relevant to the benefit-risk assessment became available during the reporting period.

17 BENEFIT EVALUATION

17.1 Important baseline efficacy information

At the beginning of the reporting period, COVID-19 ASTRAZENECA VACCINE was authorised for the prevention of COVID-19 in adults. A summary of the information supporting the efficacy and effectiveness in this authorised indication is provided in the sub-sections below.

17.1.1 Active immunisation of individuals ≥18 years old for the prevention of COVID-19

At the beginning of the reporting period, COVID-19 VACCINE ASTRAZENECA was authorised for “active immunisation of individuals > 18 years old for the prevention of COVID-19”.

COVID-19 VACCINE ASTRAZENECA is able to elicit a strong immune response capable of preventing serious symptomatic infections with SARS-COV-2, the causative agent of COVID-19, a life-threatening disease, particularly in older age groups.

COVID-19 VACCINE ASTRAZENECA has been shown to be efficacious in preventing severe disease, avoiding hospitalization and death.

A summary of new information supporting the efficacy and effectiveness of COVID-19 VACCINE ASTRAZENECA against COVID-19 is provided below.

17.2 Newly Identified Information on efficacy

During the reporting period, data analyses for study D8110C00001 was conducted to estimate the efficacy, safety and immunogenicity of the AstraZeneca Vaccine using a 6-months data cut-off (data cut-off of 31 July 2021).

The results of 6-month efficacy analysis of the D8110C00001 study are generally consistent though somewhat lower than those observed in the primary analysis, both for the overall group and for the sub-groups. Moreover, the safety profile at the 6 months data cut-off is also consistent with that observed for the previous data cut-off (data cut-off date of 05 March 2021), with the majority of AEs falling within the mild to moderate severity. The 6-month humoral immunogenicity data from this study are still under analysis.

17.2.1 Newly identified information on booster vaccination

During the report period, multiple COVID-19 vaccines had received marketing approvals and are being urgently distributed worldwide, with most being administered as a 2-dose primary series. However, the pandemic continues, with some highly vaccinated countries (≥ 70% of the population fully vaccinated) such as the UK, Singapore, and South Korea still experiencing surges in new infections. While the majority of these new infections are in the unvaccinated, breakthrough infections do occur in fully vaccinated individuals (Goldberg et al 2021, Chen et al 2021, CDC 2021 [D] and Maragakis et al 2021).

Emerging data suggest that waning protection in the months following a 2-dose primary series is contributing to the incidence of breakthrough infection.

Data supporting an AZD1222 booster dose option are supported by analysis of the University of Oxford-sponsored COV001 study as reported in Flaxman et al 2021. COV001 included a sub study of third dose booster immunogenicity and reactogenicity in 90 participants, providing robust evidence of the benefit of a booster dose and adequate assessment of risk. In participants previously vaccinated with a 2-dose course of AZD1222, data reported in Flaxman et al 2021 indicate that a third dose booster of AZD1222 administered 28 or more weeks after a second dose induces high levels of antibodies and boosts T-cell responses.

During the late breaking section of the PBRER, results from interim analysis of D7220C00001 study were available. The humoral immunogenicity data from the interim analysis of study **D7220C00001** confirm and extend the known immunogenicity profile of AZD1222. Humoral immunogenicity data from the interim analysis indicate that a booster dose of either AZD1222 or AZD2816 in seronegative participants previously vaccinated with AZD1222 or an mRNA vaccine generates a strong humoral response to SARS-CoV-2 by 28 days after the booster is administered. No emergent safety issues were identified in this study.

The COV-BOOST trial studied the use of seven different COVID-19 vaccines when given as a third 'booster' dose, including three of them also as a half dose, on participants representative of the UK population who have received 2 doses of AZD1222 or BNT162b2 (Munro et al 2021). Data from the COV-BOOST trial indicate that booster doses of COVID-19 vaccines are generally well tolerated and provide a substantial increase in vaccine-induced immune responses. The authors concluded that all vaccines studied boosted antibody and neutralising responses after an initial course of AZD1222/AZD1222, with no safety concerns, and that the substantial differences in humoral and cellular responses in combination with vaccine availability will influence policy choices for booster vaccination. In addition, heterologous boosting with AZD1222 on top of an initial course of an mRNA vaccine (BNT162b2/BNT162b2) showed similar results as after an initial course of AZD1222/AZD1222 followed by a booster, with no safety concerns.

17.2.2 Newly identified information on SARS-COV-2 variants of concern

On 26 November 2021, the WHO designated the Omicron variant (B.1.1.529) a variant of concern (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Researchers at the University of Oxford have issued a preprint regarding the neutralisation of Omicron by large panel of sera, including from convalescent patients and from vaccinees receiving 2 or 3 doses of AZD1222 or the Pfizer/BioNtech BNT16b2 vaccine (Dejnirattisai et al 2021).

AstraZeneca has also collaborated with the University of Oxford researchers who conducted these assessments and with the UKHSA, formerly called Public Health England) to analyse sera from participants in ongoing AstraZeneca-sponsored study D7220C00001 who had received 3 doses of AZD1222.

Collectively, these preliminary live virus neutralisation data suggest that 2-dose primary series immunisation with AZD1222 will likely provide limited protection against infection with the Omicron variant. These data also suggest that adding a third booster dose of AZD1222 will likely provide increased protection against infection with the Omicron variant, though still less protection than as against the original Wuhan-Hu-1 strain or other variants of concern.

Despite the higher risk of breakthrough infection with Omicron due to lower nAb titres, it is considered likely that clinically meaningful protection against hospitalisation and severe infection would be maintained. Detectable levels of nAb to the Omicron variant after boost, as well as robust humoral, cellular, and mucosal recall responses to vaccination, should offer protection from severe disease. Moreover, it is anticipated that AZD1222-induced T cell responses likely will be less affected than antibody responses, given TCR sequencing analysis has identified the immunodominant region of Spike recognised by CD8 T cells (Swanson et al 2021), which contains no mutations in the Omicron variant.

The recent surge in COVID-19 cases caused by the Omicron variant further demonstrates the benefit of vaccination either as a primary series and/or as a booster. Preliminary live virus neutralization data suggest that 2-dose primary series immunization with AZD1222 will likely provide protection, though limited, against infection with the Omicron variant. Despite the higher risk of breakthrough infection with Omicron, it is considered likely that clinically meaningful protection against hospitalization and severe infection would be maintained. Moreover, it is anticipated that AZD1222-induced T cell responses likely will be less affected than antibody responses.

Heterologous boosting with AZD1222 in individuals vaccinated with a primary series of CoronaVac resulted in a higher immune response as compared to homologous boosting with CoronaVac. Further, heterologous boosting also increased live virus neutralisation titres against both Delta and Omicron variants. These results demonstrate that a heterologous AZD1222 booster in adults with a primary vaccination of CoronaVac vaccine results in a robust humoral response without any reported safety concerns.

RHH-001 (Study Coronavac) is a phase IV randomised single-blind study conducted in Brazil among 1240 participants 18 years or older to assess the safety and immunogenicity of a third heterologous booster dose of AZD1222, BNT162b2, and AD26.COV2-S compared to a third dose homologous booster of CoronaVac in adults previously vaccinated with a primary series of CoronaVac (Clemens et al 2022).

17.3 Characterisation of benefits

The benefits of COVID-19 VACCINE ASTRAZENECA remain essentially the same as those presented in the previous PBRER. AZD1222, administered intramuscularly as two 5 x 10^{10} vp (nominal) doses at intervals from 4 weeks, has been evaluated in clinical trials spanning 6 countries and 4 continents (Europe, Africa, North America and South America), in more than 56,000 adults from 18 to 101 years of age, with broad representation in terms of sex, race, ethnicity, and the presence of risk factors for severe COVID-19. AZD1222 has been approved for conditional marketing authorization or emergency use authorization in more than 90 countries. In addition, the recent WHO Emergency Use Listing, accelerates the pathway to access in up to 145 countries through the COVAX Facility. Post-marketing data and real-world evidence studies further support the benefits of AZD1222.

The benefits of the vaccine have been demonstrated through controlled clinical studies conducted by AstraZeneca and the University of Oxford, as well as data from real world effectiveness studies. Analysis of efficacy across multiple clinical trials demonstrates that AZD1222 is effective against SARS-CoV-2 RT-PCR-positive symptomatic illness and prevents the development of severe/critical cases of COVID-19, including COVID-19 hospitalizations and deaths, confirming important advantages not only for the health of vaccine recipients, but also for the potential to reduce use of healthcare resources.

Availability of the D8110C00001 DCO3 (30 July 2021) analysis support maintenance of efficacy for at least 6-months (VE= 66.98% and a lower bound of the 95% CI of 58.87%.). Moreover, a closely similar level of efficacy is obtained across age groups. Furthermore, AZD1222 elicited a strong humoral immune response in this study.

Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis conducted separately suggest that 2-dose primary series immunization with AZD1222 will likely provide protection against infection with the Variants of Concern, including Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that AZD1222-induced T cell responses likely will be less affected than antibody responses.

Thus, the benefits of AZD1222 2-dose primary vaccinations are demonstrated by the efficacy and immunogenicity data in AstraZeneca-sponsored studies, University of Oxford-sponsored studies and from RWE studies.

Lastly, an AZD1222 booster in participants previously vaccinated with a primary series of AZD1222 or mRNA vaccine, elicits strong humoral immune responses against a range of Variants of Concern (Flaxman et al 2021, Munro et al 2021). This indicates that AZD1222 booster is likely to provide clinically meaningful protection against hospitalization and severe disease.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

The analysis of the benefit-risk balance incorporates an evaluation of the safety and efficacy/effectiveness information that became available during the reporting period, in the context of what was known previously. This evaluation involves the following:

- Critically examining information that has emerged during the reporting period to determine whether it has generated new signals, led to the identification of new potential or identified risks, or contributed to knowledge of previously identified risks.
- Critically summarising relevant new safety and efficacy/effectiveness information that could have an impact on the benefit-risk balance.
- Conducting an integrated benefit-risk analysis for all approved indication(s) based on the cumulative information available since the DIBD (where the DIBD is unknown or AstraZeneca does not have access to data from the clinical development period, the earliest possible applicable date is used as the starting point for inclusion and evaluation of the cumulative information).

- Summarising any risk minimisation actions that may have been taken or implemented during the reporting period, as well as risk minimisation actions that are planned to be implemented.
- Outlining plans for signal or risk evaluations, including timelines and/or proposals for additional pharmacovigilance activities.

18.1 Benefit-risk context - medical need and important alternatives for approved indications

A description of the medical need for COVID-19 VACCINE ASTRAZENECA and important alternatives available for the approved indication is provided below.

18.1.1 Active immunisation of individuals ≥ 18 years old for the prevention of COVID-19

Medical need for the product

The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts.

As of 18 December 2021, over 271 million confirmed cases of COVID-19 infection have been diagnosed globally with more than 5.3 million deaths (WHO 2021a). By 17 December 2021, there had been over 28 million confirmed cases of COVID-19 infection and over 332 thousand deaths in the EU/European Economic Area (ECDC 2021).

In clinical trials COVID-19 VACCINE ASTRAZENECA confers protection against severe cases of COVID-19, as well as most COVID-19 hospitalisations, thus highlighting an important advantage, not only for the health of vaccine recipients, but also for the potential of reducing utilization of healthcare resources. Overall, vaccination with COVID-19 VACCINE ASTRAZENECA has shown to be a critical intervention in preventing COVID-19 and its associated risk of severe morbidity and mortality, both for the individual and for the broader public health.

Older adults and those with pre-existing disease are at higher risk of severe COVID-19 outcomes and have the greatest unmet medical need among the general population (Gallo Marin B.et al 2021).

Data obtained from the ongoing COVID-19 VACCINE ASTRAZENECA clinical trials described in Section 7 and Section 8 have shown consistent VE against COVID-19, both in participants with or without background comorbidities.

The AZD1222 vaccine, an adenoviral-based vaccine, has been granted a conditional marketing authorization or emergency use authorization for the prevention of COVID-19 in adults 18 years and older in more than 90 countries, and with the Emergency Use Listing

granted by the WHO, the vaccine may be accessible in up to 145 countries through the COVAX Facility.

In addition, emerging data suggest that waning protection in the months following a 2-dose primary series is contributing to the incidence of breakthrough infection. Analyses from Israel and the UK (Levin et al 2021, Andrews et al 2021), 2 of the countries with the earliest and most-rapid vaccine rollouts, and from the US show waning of immunogenicity and efficacy by 6 months following completion of a primary vaccination series (Cohn et al 2021). Besides waning immunity against existing variants, another concern is that as vaccination and natural infection increase immune pressure against the virus, novel SARS-CoV-2 variants of concern will continue to emerge. These variants emerge as a result of high rate of mutation, replication in infected individuals, improved transmissibility, and immune escape.

There is a clear unmet and urgent medical need to maintain and/or increase protection in vaccinated individuals in the face of waning immunity and emerging variants of SARS-CoV-2. For many infectious diseases, multiple or additional 'booster' doses beyond those prescribed by the original vaccination protocol are a standard part of the vaccination schedule. For example, booster vaccines are given for tetanus, diphtheria, and polio (NHS 2021). Boosters can help to elevate the level of antibodies and memory immune cells, and in some instances, strengthen their potency (Callaway 2021).

As recommendations and regulatory authorizations for booster dosing with COVID-19 vaccines continue to expand, the authorization of AZD1222 for booster vaccination will help address the unmet demand for COVID-19 vaccine doses, when a substantial number of people, particularly in low and low-to-middle income countries, have not received or completed a primary vaccination series (Ritchie et al 2020).

Important alternatives available

In December 2020, the first COVID-19 vaccine candidate (COVID-19 mRNA Vaccine BNT162b2) was authorised in the UK on a temporary basis under Regulation 174 of the Human Medicine Regulations 2012 and granted conditional marketing authorisation in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 16 years of age. That same month, Vaxzevria (previously COVID-19 Vaccine AstraZeneca) temporary authorisation was also issued under UK Regulation 174 for individuals ≥ 18 years of age. In January 2021, Vaxzevria and COVID-19 Vaccine Moderna were granted conditional marketing authorisation in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 18 years of age. Conditional marketing authorisation in the EU was also granted for COVID-19 Vaccine Janssen in March 2021 and for Nuvaxovid COVID-19 Vaccine (recombinant, adjuvanted) (Novavax CZ a.s.) in December 2021. Subsequently, and as of 07 October 2021, at least 13 different vaccines, utilizing 4 platforms, have been administered globally (WHO 2021a). As of October 2021,

136 candidate vaccines are in clinical development and 194 are in nonclinical investigation (WHO 2021).

The recent surge in COVID-19 cases caused by the Omicron variant further demonstrates the benefit of vaccination either as a primary series and/or as a booster. Preliminary live virus neutralization data suggest that 2-dose primary series immunization with AZD1222 will likely provide protection, though limited, against infection with the Omicron variant. Despite the higher risk of breakthrough infection with Omicron, it is considered likely that clinically meaningful protection against hospitalization and severe infection would be maintained. Moreover, it is anticipated that AZD1222-induced T cell responses likely will be less affected than antibody responses (see Omicron assessment report, Module 1.11.3).

18.2 Benefit-Risk Analyses evaluation

An evaluation of the benefit-risk profile for the use of COVID-19 VACCINE ASTRAZENECA in the authorised indications cited in Section 17.1 (Important baseline efficacy/effectiveness information) is provided below.

18.2.1 Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

18.2.1.1 Context of use of the medicinal product

The COVID-19 epidemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Containment measures have failed to stop the spread of virus, which has resulted in pandemic levels. World-wide efforts to develop effective vaccines against SARS-CoV-2 are ongoing. Given the extent and continued rapid pace of infection, severity of the pandemic's medical and socioeconomic impact, and the supply challenges associated with a global vaccination program, multiple vaccines are needed. AZD1222 was developed to address this public health need.

The COVID-19 VACCINE ASTRAZENECA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of COVID-19 VACCINE ASTRAZENECA complete the vaccination course with COVID-19 VACCINE ASTRAZENCA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with COVID-19 VACCINE ASTRAZENECA at least 3-months after completing the primary 2-dose vaccination course (homologous boosting). During the Late-breaking period, the CDS was updated to note that COVID-19 VACCINE ASTRAZENECA may be given as a booster dose after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting) (see Section 14).

There has been no new data or information received during the reporting period that impacts the previously established efficacy and effectiveness of COVID-19 VACCINE ASTRAZENECA in the approved indication of prevention of COVID-19 in adults 18 years of age and older.

Additionally, analysis of efficacy at the 6-month data cut-off, demonstrated that vaccine efficacy of AZD1222 was maintained up to 6 months post first dose. The results of the 6-month humoral immunogenicity are still under analysis.

Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis conducted separately suggest that 2-dose primary series immunization with AZD1222 will likely provide protection against infection with the current Variant of Concern, Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that AZD1222-induced T cell responses likely will be less affected than antibody responses.

With the COVID-19 pandemic causing a global health crisis with severe illness, hospitalisations and death in many individuals, in addition to major disruption to healthcare systems, it is clear that multiple vaccines with a positive benefit-risk are needed. With its proven effect in preventing COVID-19 and related hospitalisations, including protection against current variants, COVID-19 VACCINE ASTRAZENECA is considered appropriate to address this urgent unmet medical need. Moreover, the easy storage and handling of the COVID-19 VACCINE ASTRAZENECA formulation is considered to be an important additional benefit that enables wide access to the vaccine.

In conclusion , the overall benefits of AZD1222 in the prevention of COVID-19 with robust efficacy overall, in a wide array of subgroups, including adults ≥ 65 years of age and persons with at least one comorbidity at enrolment, and in the prevention of severe/critical COVID-19 illness and COVID-19 related emergency department visits and deaths continue to outweigh risks from adverse events, including the very rare risk of thrombosis in combination with thrombocytopenia identified through post-marketing safety reports.

18.2.1.2 Considerations relating to key benefit(s)

There remains a public health need for vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Since development of AZD1222 in 2019, at least 13 different vaccines utilizing 4 platforms, including AZD1222, have been authorized or approved globally (WHO 2021). Despite the availability of authorized/approved COVID-19 vaccines, surges in COVID-19 cases continue to occur. There remains a need for vaccines based on an adenoviral vector platform, such as AZD1222, given its efficacy and/or effectiveness humoral immunogenicity against a spectrum of VOC.

Moreover and to a lesser extent there remains a need for alternative vaccines for populations who may be hypersensitive to mRNA-based vaccines, including those that may have an allergy to one of the mRNA vaccine components or had a severe allergic reaction to the first dose of mRNA vaccine (Sokolowska et al 2021, Wolfson et al 2021), and those who prefer not to receive an mRNA vaccine for personal reasons.

World Health Organization provided interim guidance on 30 July 2021 for the generic group of COVID-19 Vaccine (ChAdOx1-S [recombinant]) for considering data emerging from AstraZeneca's core clinical trials and post-introduction effectiveness and safety monitoring. The guidance was based on an initial evidence document developed by Oxford University and AstraZeneca. In additional to proven efficacy and a good safety profile obtained from clinical trial data, several research studies conducted in the real-world setting have consistently demonstrated that COVID-19 VACCINE ASTRAZENECA effectiveness has played an important role in saving lives since the start of vaccination campaigns worldwide (CDC 2021 [A]). More specifically, vaccine effects were seen from 14 to 20 days after vaccination, reaching an effectiveness of 60% (95% CI: 41, 73) from 28 to 34 days and further increasing to 73% (95% CI: 27, 90) from Day 35 onwards. In addition to protection against symptomatic disease, vaccination with 1 dose of COVID-19 VACCINE ASTRAZENECA resulted in an additional 37% (95% CI: 3, 59) lower risk of emergency hospitalisation, indicating that a single dose of COVID-19 VACCINE ASTRAZENECA is approximately 80% effective at preventing hospitalisation. Furthermore, a national prospective cohort study comprising nearly the entire Scottish population demonstrated that a single dose of COVID-19 VACCINE ASTRAZENECA was associated with substantial protection against COVID-19-related hospitalisation. Peak VE for COVID-19 VACCINE ASTRAZENECA was 94% (95% CI: 73, 99) at 28 to 34 days post-vaccination (Vasileiou et al 2021). With the COVID-19 pandemic causing a global health crisis with severe illness, hospitalisations and death in many individuals, in addition to major disruption to healthcare systems, it is clear that multiple vaccines with a positive benefit-risk are needed. With its proven effect in preventing COVID-19 and related hospitalisations, together with a favourable safety profile, COVID-19 VACCINE ASTRAZENECA is considered appropriate to address this urgent unmet medical need. Moreover, the easy storage and handling of the COVID-19 VACCINE ASTRAZENECA formulation is considered to be an important additional benefit that enables wide access to the vaccine.

In conclusion, the benefit-risk profile of COVID-19 VACCINE ASTRAZENECA has been shown to be consistently favourable across the clinical development programme and in published real-world evidence studies. The benefit-risk profile is favourable for the proposed indication in adults from age 18 years and older, including adults from age 65 years and above, as well as those with comorbidities.

18.2.1.3 Considerations relating to risk

The important identified risks associated with COVID-19 VACCINE ASTRAZENECA are characterised in detail in Section 16.4.

At the end of the reporting period, one Important identified risk was included in the Core RMP: Thrombosis in combination with thrombocytopenia In addition, three Important potential risks were included in the Core RMP: Immune-mediated neurological conditions, VAED, and CVST without thrombocytopenia.

Considerations regarding the key risk are summarised below:

- **Thrombosis in combination with thrombocytopenia**: A very rare and serious combination of thrombosis and thrombocytopenia, including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with AZD1222 during post-authorisation use. The majority of the events occurred within the first 21days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to the first dose. Based on the available data, thrombosis in combination with thrombocytopenia is considered a very rare adverse reaction of AZD1222. CDS reflects AstraZeneca's position on this risk.
- **Anaphylaxis:** The identified risk of anaphylaxis was based on a reasonable possibility of a causal association between COVID-19 VACCINE ASTRAZENECA treatment and anaphylaxis. CDS reflects AstraZeneca's position on this risk.
- **Immune-mediated neurological conditions:** There is a theoretical concern that vaccination could be associated with immune-mediated neurological conditions. Very rare events of demyelinating disorders were reported in the COVID-19 VACCINE ASTRAZENECA clinical development programme and in the post-marketing use, however, there is no evidence suggesting a causal relationship between COVID-19 VACCINE ASTRAZENECA and demyelinating disorders. Severe neurological conditions may result in persistent or significant disability or incapacity and require early detection, careful monitoring, and timely medical intervention. CDS reflects AstraZeneca's position on this risk.
- **CVST without thrombocytopenia:** Events of cerebrovascular venous and sinus thrombosis (CVST) without thrombocytopenia have been reported very rarely in the post-authorisation setting following vaccination with AZD1222.

  The exact mechanism of CVST without thrombocytopenia following administration with AZD1222 is unknown. There are no known risk factors for the development of CVST without thrombocytopenia following vaccination. Events of CVST without thrombocytopenia may require different treatment approaches than thrombosis in combination with thrombocytopenia (eg, use of heparin or warfarin).

  Based on the available data, a causal association has not been established between AZD1222 and CVST without thrombocytopenia. However, such events are considered an important potential risk and CDS reflects AstraZeneca's position on this risk.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks continue to suggest an overall positive benefit-risk profile for the use of COVID-19 VACCINE ASTRAZENECA. The data gathered during the reporting period of this PSUR did not provide any additional evidence which would alter the efficacy or safety evaluation of COVID-19 VACCINE ASTRAZENECA.

18.2.1.4 Strengths, weaknesses, and uncertainties of the evidence

The efficacy results have been confirmed in one large study conducted in the US, Chile and Peru and from the pooled analysis of 4 Oxford University Sponsored studies (COV 001, COV002, COV003 & COV005 studies) all of which are randomised, controlled trials.

The study design and VE definitions used the WHO clinical progression scale (WHO 2021). All data from participants with SARS-CoV-2 virologically positive results from RT-PCR or other nucleic acid amplification tests are assessed by a blinded adjudication committee and the events adjudicated as symptomatic-primary events will be used for all analyses and also determined by the adjudication committee, will be utilized to assess the severity of disease.

The data have limitations, particularly with regard to applicability to other populations. There is limited information on treatment with the vaccine while pregnant or breastfeeding, as well as for use in patients with other diseases such as immunosuppression. However, noninterventional and one interventional (immunocompromised patients) studies are underway to study some of these populations.

The 6-month VE efficacy data now available support the conclusion that AZD1222 continues to provide good efficacy against COVID-19 for at least 6 months.

AZD1222 confers a strong immunogenicity response when administered as a booster both in the homologous or heterologous primary series settings.

Interaction with other medicinal products and other forms of interaction have not been formally studies, nor has concomitant administration of COVID-19 VACCINE ASTRAZENECA with other vaccines, such as flu vaccines.

Another population with limited data are those patients with autoimmune or inflammatory disorders. This population is potentially at risk of developing a more severe manifestation of COVID-19. Although there is no evidence that the safety profile of this population receiving COVID-19 VACCINE ASTRAZENECA will be different to that of the general population, the data is limited. As this population has been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability, proactive data collection in this population receiving COVID-19 VACCINE ASTRAZENECA is underway.

18.2.1.5 Methodology and reasoning used to develop the benefit-risk evaluation

A qualitative assessment of the benefit-risk balance for the use of COVID-19 VACCINE ASTRAZENECA for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥18 years of age has been performed.

Conclusions on efficacy from the COVID-19 VACCINE ASTRAZENECA clinical development programme, in particular from the pooled analysis of Studies COV001, COV002, COV003, COV005 and the preliminary analysis of the study within the sites in the US, Chile, and Peru, provide the evidence of the key benefits associated with the use of COVID-19 VACCINE ASTRAZENECA in the approved indication. Key benefits are those that are considered to have a substantial positive impact on the benefit-risk balance.

AstraZeneca's pharmacovigilance system provides the framework for the identification of any risks associated with the use of COVID-19 VACCINE ASTRAZENECA in the approved indication. All information that has emerged during the reporting period been reviewed and evaluated by AstraZeneca, irrespective of reporting source, seriousness or causality. This has included an analysis of, clinical trials, literature studies, safety topics that are kept under close surveillance, as well as an assessment of any new safety issues.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks give an overall positive benefit-risk profile for the use of COVID-19 VACCINE ASTRAZENECA. The data gathered during the reporting period of this PBRER did not provide any additional evidence which would alter the efficacy or safety evaluation of COVID-19 VACCINE ASTRAZENECA.

19 CONCLUSIONS AND ACTIONS

COVID-19 VACCINE ASTRAZENECA is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥ 18 years of age, as described in previous sections.

During the reporting period, the clinical database significantly expanded with 21587 patients from the US, Chile, and Peru that had received COVID-19 VACCINE ASTRAZENECA. Despite different locations, populations, periods of time, and vaccine administration, the original VE estimate was confirmed, and the VE point estimate was higher in the elderly population compared to the general population.

There were no significant safety findings from any of the AstraZeneca-sponsored or Oxford-sponsored clinical trials with AZD1222. AstraZeneca is not aware of any safety signals arising for AZD1222/COVID-19 VACCINE ASTRAZENECA from any other studies conducted by AstraZeneca partner companies.

During the reporting period, the Core RMP was updated to include CVST without thrombocytopenia as an Important potential risk. In addition, the CDS was updated to include information regarding CVST without thrombocytopenia (Section 4.4). In addition, Section 4.8 of the CDS was updated to include information regarding reactogenicity in participants who received a booster dose in the COV001 Study. Post-data lock CDS Section 4.6 was updated to reflect the most current non-clinical, clinical and post-authorization data regarding the use of COVID-19 VACCINE ASTRAZENECA during pregnancy and while breastfeeding to consider the use of the vaccine during pregnancy when the benefits outweigh the risks. In addition, AstraZeneca has validated signals of hypoaesthesia/paraesthesia and GBS. The CDS is currently under revision to include hypoaesthesia and paraesthesia as ADRs in Section 4.8 and this is in the late-stage of being finalized. AstraZeneca is further reviewing the signal of GBS as part of internal signal evaluation processes and will provide the conclusions and any recommended actions within the next PSUR.

In addition, GBS and Thrombocytopenia, including immune thrombocytopenia were added to the EU RMP for COVID-19 VACCINE ASTRAZENECA as a result of impositions. Finally, due to global health authority impositions, local labelling documents underwent revisions during the review period to incorporate CLS, GBS, Transverse myelitis, and Thrombocytopenia, including immune thrombocytopenia.

The benefit of vaccination COVID-19 VACCINE ASTRAZENECA has been weighed against the safety experience in the clinical programmes as well from post-authorization use. The data received during this reporting period, combined with analyses of the cumulative efficacy and safety data available, does not indicate a change in the positive benefit-risk profile of COVID-19 VACCINE ASTRAZENECA. It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for COVID-19 VACCINE ASTRAZENECA.

20 APPENDICES TO THE PBRER

A full list of Appendices and Regional Appendices is provided in the List of Appendices presented in the Table of Contents.

Where submitted, Regional Appendices R1 to R10 provide information meeting local requirements.

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