Periodic Benefit-Risk Evaluation Report	
Medicinal Product	COVID-19 VACCINE ASTRAZENECA (AZD1222)
Date	23 August 2021

COVID-19 VACCINE ASTRAZENECA (AZD1222) / VAXZEVRIA™

Periodic Benefit-Risk Evaluation Report

Period covered: 29 December 2020 to 28 June 2021

International birth date: 29 December 2020 (United Kingdom)

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

COVID-19 VACCINE ASTRAZENECA (AZD1222) / VAXZEVRIA™

Periodic Benefit-Risk Evaluation Report

Period covered:	29 December 2020 to 28 June 2021	
International birth date:	29 December 2020 (United Kingdom)	
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 December 2020 to 28 June 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 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). 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. 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.
- **Marketing approvals:** As of 28 June 2021, COVID-19 VACCINE ASTRAZENECA has been approved either for conditional marketing authorisation (CMA) or emergency use authorisation (EUA) in more than 90 markets managed by AstraZeneca (around 60 Markets including EU) and AstraZeneca Partners (around 30 markets) including, Serum Institute of India (SII), R-pharm, Fiocruz and Verity Pharmaceuticals.
- **Actions taken or proposed for safety reasons:**
  - Anaphylaxis, Thrombosis in combination with thrombocytopenia, and Thrombocytopenia (TCP) have been added as adverse drug reactions (ADRs) in the Core Data Sheet (CDS) and European Union (EU) Summary of Product Characteristics (SmPC). In addition, a Warning and Precaution and Contraindication has been added to the CDS and SmPC regarding thrombosis in combination with thrombocytopenia. Anaphylaxis and Thrombosis in combination with thrombocytopenia has been added as an Important Identified Risk in the Core and EU Risk Management Plans (RMP).
  - AstraZeneca received a labelling imposition for the EU SmPC to contraindicate vaccination with COVID-19 VACCINE ASTRAZENECA in people who have previously had Capillary Leak Syndrome (CLS), to add CLS to Warnings and Precautions and to add CLS as an ADR. AstraZeneca received a similar imposition from Medicines and Healthcare Products Regulatory Agency (MHRA), Therapeutic Goods Administration (TGA) and Canada.
  - AstraZeneca received an imposition from Pharmacovigilance Risk Assessment Committee (PRAC) to include “Thrombocytopenia with associated bleeding” as an Important potential risk in the safety concerns of the EU RMP. Post the reporting period, the EU RMP was updated to incorporate this revision and to add Acute macular neuroretinopathy (AMN)/Acute macular outer retinopathy (AMOR), Paracentral acute middle maculopathy (PAMM), and Paraesthesia and

dysaesthesia as adverse events of special interest (AESIs). The review of this variation is ongoing.

- **Safety changes to Reference Safety Information:**
  The following were identified during the reporting period as possible adverse reactions associated with COVID-19 VACCINE ASTRAZENECA and included in the CDS.
  - On 01 March 2021 Sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) were updated to include information on anaphylaxis and hypersensitivity including anaphylaxis respectively.
  - On 02 April 2021 and 06 April 2021 Section 4.4 (Special warnings and special precautions for use) was updated to include serious thrombosis with TCP.
  - On 19 April 2021 Sections 4.3 (Contraindications), 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) were updated to include information on thrombosis in combination with thrombocytopenia.
  - On 26 April 2021 Section 4.6 (Pregnancy and lactation) was updated to include pregnancy and lactation based on non-clinical studies, Section 5.3 (Pre-clinical safety data) was updated to include pre-clinical studies.
  - On 27 May 2021 Section 4.8 (Undesirable effects) was updated to include D8110C00001 study data.
  - On 17 June 2021, Sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) of the CDS was updated to include additional details regarding Thromboembolism and TCP.
- **Estimated cumulative exposure of clinical trial subjects:** Approximately 57565 healthy volunteers have been enrolled into the clinical development programme, of which approximately 34515 have received at least one dose of COVID-19 VACCINE ASTRAZENECA.
- **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 for the EU, United Kingdom (UK), India, Canada, Australia and the Philippines. The cumulative number of doses administered in these territories/regions was confirmed as being over 390 million doses. The number of doses distributed globally are over 588 million doses cumulatively.
- **Late-breaking information:** Post the reporting period AstraZeneca received an imposition to add a warning about Guillain-Barré Syndrome (GBS) to the EU SmPC. AstraZeneca received a similar imposition from Medicines and Healthcare Products Regulatory Agency (MHRA).

  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 indications. There were no important identified risks prior to the reporting

period. During the reporting period, the Core and EU RMPs were updated to include Thrombosis in combination with thrombocytopenia/TTS. In addition, the EU RMP was updated to include Anaphylaxis as an Important Identified Risk and Thrombosis as an Important Potential Risk. Furthermore, AstraZeneca received an imposition from PRAC to include "Thrombocytopenia with associated bleeding" as an Important potential risk in the safety concerns of the EU RMP, which was updated and submitted post the reporting period.

The important risks are considered manageable based on risk minimisation measures currently utilised in the clinical studies in conjunction with appropriate labelling, and ongoing AstraZeneca pharmacovigilance activities.

- **Conclusions and actions**: The data received during this reporting period 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.

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LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
ACO	Addendum to the Clinical Overview
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AEs	Adverse Events
AESI	Adverse Event of Special Interest
AMN	Acute Macular Neuroretinopathy
AMOR	Acute Macular Outer Retinopathy
ARDS	Acute Respiratory Distress Syndrome
AUH	Aarhus University Hospital
AZ	AstraZeneca
BC	Brighton Criteria
BCC	Brighton Collaboration criteria
BP	Blood Pressure
CDC	Centres for Disease Control and Prevention
CDS	Core Data Sheet
ChAdOx1	Chimpanzee Adenovirus
CI	Confidence Interval
CLS	Capillary Leak Syndrome
CN	Cranial Nerve
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
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DSRU	Drug Safety Research Unit
DVT	Deep Vein Thrombosis

Abbreviation or special term	Explanation
EAS	Enhanced Active Surveillance
EEA	European Economic Area
EEG	Electroencephalography
EMA/EMEA	European Medicinal Agency
ES_SIDIAP_PC	Spain Information System for the Development of Research in Primary Care
EU	European Union
EUA	Emergency Use Authorizations
EVDAS	EudraVigilance Data Analysis System
FDA	Food and Drug Administration
FLAIR	Fluid-Attenuated Inversion Recovery
FSI	First Subject In
FVS	Fully Vaccinated Analysis Set
GBS	Guillain-Barre syndrome
GI	Gastrointestinal
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Hazard Ratio
IBD	International Birth Date
ICSR	Individual Case Safety Reports
ICU	Intensive Care Unit
IM	Intramuscular
IMID	Immunomodulators
IR	Incidence Rate
ISTH	The International Society on Thrombosis and Haemostasis
IT_ARS	Regional Health Agency of Tuscany
IVIG	Intravenous Immunoglobulin
LD	Low Dose
LDL	Low Density Lipoprtein
LDSD	1 low dose and 1 standard dose
LSO	Last Subject Out
ME	Myalgic Encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MELAS	Mitochondrial Encephalopathy Lactic Acidosis And Stroke-Like Episodes
MenACWY	Meningococcal Vaccine

Abbreviation or special term	Explanation
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS-C/A	Multisystem Inflammatory Syndrome In Children/Adults
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSSR	Monthly Summary Safety Report
NCS	Nerve Conduction Study
NHS	National Health Service
O/E	Observed/Expected
OHDSI	Observational Health Data Science and Informatics
PAHO	Pan American Health Organization
PAMM	Paracentral Acute Middle Maculopathy
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary Embolism
PF-4	Platelet Factor 4
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
PY	Person Years
RBD	Receptor-Binding Domain
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RoR	Reporting Odds Ratio
RT-PCR	Real-Time Polymerase Chain Reaction
RW	Risk Window
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SD	Standard Dose
SDSD	2 Standard Doses
SII	Serum Institute of India
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class

Abbreviation or special term	Explanation
SOT	Solid Organ Transplantation
SSI	Staten Serum institute
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCP	Thrombocytopenia
TGA	Therapeutic Goods Administration
TTO	Time To Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
UMC	Uppsala Monitoring Centre
USA/US	United States of America/United States
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
WHO	World Health Organization

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 December 2020 and 28 June 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 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 immunisation of individuals ≥18 years for the prevention of COVID-19.

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. 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 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 authorized for emergency use in the United Kingdom (UK) on 29 December 2021 under Regulation 174A(2) of the Human Medicine Regulation with indication of active immunisation of individuals ≥18 years for the prevention of COVID-19 in UK. The vaccine received conditional marketing authorization in the EU on 29 January 2021.

As of 28 June 2021, COVID-19 VACCINE ASTRAZENECA has been approved either for conditional marketing authorisation (CMA) or emergency use authorisation (EUA) in more

than 90 markets managed by AstraZeneca (around 60 Markets including EU) and AstraZeneca Partners (around 30 markets) including, Serum Institute of India (SII), R-pharm, Fiocruz and Verity Pharmaceuticals.

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

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

During the reporting period Anaphylaxis and Thrombosis in combination with Thrombocytopenia, and Thrombocytopenia (TCP) were added as adverse drug reactions (ADRs) in the Core Data Sheet (CDS). In addition, a Warning and Precaution and Contraindication regarding Thrombosis in combination with thrombocytopenia have been added to the CDS. The Core and EU Risk Management Plan (RMP)s were updated accordingly. Full description of changes made to the COVID-19 VACCINE ASTRAZENECA CDS during the review period are provided in Section 4 and changes made to the COVID-19 VACCINE ASTRAZENECA Core RMP occurring during the review period are provided in Section 16.

An imposition was received from the European Medicinal Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) to add Capillary Leak Syndrome (CLS) as a Contraindication to Section 4.3 of the EU SmPC. AstraZeneca received similar impositions from Health Canada, the Medicines and Healthcare Products Regulatory Agency (MHRA), and the Therapeutic Goods Administration (TGA).

Post the reporting period, AstraZeneca received an imposition to add a warning about Guillain-Barré Syndrome (GBS) to the EU SmPC. AstraZeneca received a similar imposition from Medicines and Healthcare Products Regulatory Agency (MHRA).

AstraZeneca received an imposition from EMA PRAC to include “Thrombosis with associated bleeding” as an Important potential risk and add Acute macular neuroretinopathy (AMN)/Acute macular outer retinopathy (AMOR), Paracentral acute middle maculopathy (PAMM), and Paraesthesia and dysaesthesia as adverse events of special interest (AESIs). Refer to Section 14 (Late Breaking) for further information regarding these impositions.

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 21 December 2020.

During this reporting period, the COVID-19 VACCINE ASTRAZENECA CDS was updated 7 times to include the safety-related changes summarised in Table 1.

Table 1 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECA 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
01 March 2021	**CDS Section 4.4– Special warnings and special precautions for use** Hypersensitivity **including anaphylaxis** Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of COVID-19 VACCINE ASTRAZENECA**.** Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. **A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first dose of COVID-19 VACCINE ASTRAZENECA.** **CDS Section 4.8– Undesirable effects** Overall summary of the safety profile: The overall safety of VAXZEVRIA is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, **24244** participants ≥18 years old had been randomised and received either VAXZEVRIA or control. Out of these, **12282** received at least one dose of VAXZEVRIA, **with a median duration of follow-up of 4.5 months.** Demographic characteristics were generally similar among participants who received VAXZEVRIA and those who received control. Overall, among the participants who received VAXZEVRIA, **89.8**% were aged 18 to 64 years and **10.2**% were 65 years of age or older. The majority of recipients were White	Further information regarding this change is presented in Section 16.2.5.1.

Table 1 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECA 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
	(75.5%), **9.8**% were Black and **3.7**% were Asian; 55.8% were female and 44.2% male.	
02 April 2021	**CDS Section 4.4 – Special warnings and special precautions for use** Addition of text to alert healthcare providers and vaccine recipients to the very rare events of serious thrombosis with thrombocytopenia	Further information regarding this change is presented in Section 16.3.2.1.
06 April 2021	**CDS Section 4.4 – Special warnings and special precautions for use** Further revisions to text relating to very rare events of serious thrombosis with thrombocytopenia	Further information regarding this change is presented in Section 16.3.2.1.
19 April 2021	**CDS Section 4.3 - Contraindications** Addition of a contraindication: Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine. **CDS Section 4.4 – Special warnings and special precautions for use** Revisions to text related to events of thrombosis occurring with thrombocytopenia **CDS Section 4.8 – Undesirable effects** Addition of the following under Post-authorization experience: Vascular disorders: A very rare and serious combination of thrombosis and thrombocytopenia	Further information regarding this change is presented in Section 16.3.2.1.

Table 1 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECA 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
26 April 2021	**CDS Section 4.6 – Pregnancy and lactation** Addition of results from COVID-19 VACCINE ASTRAZENECA non-clinical studies. **CDS Section 5.3 – Pre-clinical safety data** Revised to include most recent COVID-19 VACCINE ASTRAZENECA non-clinical studies.	Not applicable
27 May 2021	**CDS Section 4.8 – Undesirable effects** Addition to add a short summary of safety data from Study D8110C00001	Not applicable
17 June 2021	**CDS Section 4.4 – Special warnings and special precautions for use** Thromboembolism and thrombocytopenia: Added clarification that the concept “thrombosis in combination with thrombocytopenia” also covers Thrombosis with Thrombocytopenia Syndrome (TTS). Edited text on risk factors to make it specific to thromboembolism in combination with thrombocytopenia. Changed risk window of developing thromboembolism and thrombocytopenia from 14 days to 21 days Added wording advising that individuals presenting with either thrombocytopenia or thrombosis within 21 days of vaccination be investigated for signs of thrombosis in combination with thrombocytopenia. Added wording advising HCPs to seek specialist advice to diagnose and treat thrombosis in combination with thrombocytopenia. **CDS Section 4.8 – Undesirable effects** Summary of post authorization data	Further information regarding this change is presented in Section 16.3.2.1.

Table 1 Summary of safety-related changes to the COVID-19 VACCINE ASTRAZENECA 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
	For the combination of thrombosis and thrombocytopenia: added clarification that the concept of combination of thrombosis and thrombocytopenia also includes TTS. Added thrombocytopenia with frequency "very rare" and included a clarifying note regarding the age group (18-59) for which the majority of events were reported.	

CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, HCP Healthcare Professional, PBRER Periodic Benefit-Risk Evaluation Report, 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 17 June 2021, is the reference for both the benefit and risk sections.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 2, based on actual enrolment/randomisation schemes for ongoing trials.

Table 2 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
COVID-19 VACCINE ASTRAZENECA	34515
AZD2816*	11
MenACWY	10945
Rabies vaccine	135
Placebo	11959

Cumulative numbers from initiation of the first clinical trials up to 28 June 2021.

*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.

COVID-19 Coronavirus Disease 2019.

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 3 and Table 4, respectively.

Table 3 Estimated cumulative subject exposure to COVID-19 VACCINE ASTRAZENECA 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	23584	23959	47543
>=65	5545	4117	9662
Missing	70	29	99
Total	29331	28234	57565

Data from completed and ongoing clinical trials as of 28 June 2021.
All dosed subjects are included. Gender is based on biological sex at birth in COV008 study.
COVID-19 Coronavirus Disease 2019.

Table 4 Estimated cumulative subject exposure to COVID-19 VACCINE ASTRAZENECA from ongoing clinical trials by racial group

Racial group	**Number of subjects**
American Indian Or Alaska Native	1279
Asian	2536
Black Or African American	5172
Native Hawaiian Or Other Pacific Islander	81
White	44217
Other	1568
Multiple Categories Checked	1853
Missing	589
Total	57295

Data from completed and ongoing clinical trials as of 28 June 2021. All dosed subjects are included.
Other race category includes multiple race categories.
270 subjects from COV004 excluded as race was not collected in this study.
COVID-19 Coronavirus Disease 2019.

5.2 Cumulative and interval patient exposure from marketing experience

The post-marketing patient exposure data is presented by both the number of doses distributed and the number of doses administered. All exposure is intended for the same indication and

route of administration. For this aggregate report, interval and cumulative dose distribution data are the same due to the time period under review (29 December 2020 to 28 June 2021).

Section 5.2.1.1 below describes doses distributed, which includes dose distribution information across all markets, including countries where AstraZeneca is the Marketing Authorisation Holder and countries where supported by licence partners.

Section 5.2.1.2 below describes doses administered to vaccinees, which is a more specific measure of exposure at the vaccinee-level. This measure allows capture of demographic information, but it requires gathering information at a country level from relevant health departments. To date, only specific countries and regions have made demographic data available, although AstraZeneca continues to work on collecting this data from all countries that administer the COVID-19 VACCINE ASTRAZENECA.

5.2.1 Post-approval (non-clinical trials) exposure

5.2.1.1 Patient exposure - doses distributed

Since 29 December 2020 (IBD) to 25 June 2021, patient exposure by doses distributed to COVID-19 VACCINE ASTRAZENECA was estimated at over 500 million doses in over 70 countries. The countries include approximately 40 countries managed by AstraZeneca partners. The regional dose distribution data is presented in Table 5.

Table 5 COVID-19 VACCINE ASTRAZENECA Doses Distributed by Region and Exposure from 29 December 2020 through 25 June 2021[a]

Region	Exposure by doses distributed (29 December 2020 through 25 June 2021)
Europe	128543960
International	84862800
North America	2474500
Fiocruz[b]	1725800
R-Pharm[c]	54793750
Serum Institute of India[d]	315884300
Total	**588285110**

[a] Distribution data is received on a weekly basis. 25 June 2021 was the closest available distribution data to the data-lock point of this PBRER (28 June 2021)

[b] Data from Fiocruz is as of 18 June 2021.

[c] Data from R-Pharm is as of 25 June 2021.

[d] Data from Serum Institute of India is as of 15 June 2021.

COVID-19 Coronavirus Disease 2019.

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

AstraZeneca works directly with health departments in individual countries to determine the number of doses administered. Data has either been provided to AstraZeneca directly from Government bodies or it has been sourced from country-specific websites. Administration data from the licence partners (SII, Fiocruz and R-Pharm) have not been provided directly to AstraZeneca. As a result, the dose administered data in this report is less than the doses distributed, because administration data has not been made available to AstraZeneca from all markets where the COVID-19 VACCINE ASTRAZENECA is authorised.

Table 6 below presents the cumulative exposure for COVID-19 VACCINE ASTRAZENECA since 29 December 2020 by each of the two doses administered for the reporting countries.

Table 6 COVID-19 VACCINE ASTRAZENECA Cumulative Exposure Based on Doses Administered by Region/Country since 29 December 2020

Region	Cumulative		
	Dose 1	Dose 2	Regionwide Total
European Union[a]	38262741	16669122	54931863
United Kingdom[a]	24612474	21279831	45892305
India[b]	280206466		280206466
Canada[c]	2596923		2596923
Philippines[a]	2170266	452352	2622618
Australia[a]	4138173	453227	4591400
Total[d]	**69183654**	**38854532**	**-**
Grand Total[e]	**390841575**		

[a] Administration data for the European Union, United Kingdom, Philippines, and Australia is current up to 27 June 2021.

[b] Administration data from India is current up to 28 June 2021.

[c] Administration data from Canada is current up to 25 June 2021.

[d] The total contains values excluding India and Canada.

[e] Grand total contains values including India and Canada.

COVID-19 Coronavirus Disease 2019.

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 7 and Table 8, respectively.

Table 7 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 7 COVID-19 VACCINE ASTRAZENECA Cumulative Exposure Based on Doses Administered by Age Group from 29 December 2020 through 27 June 2021[a]

Age group	Cumulative		
	Dose 1	Dose 2	Total
18-24	572593	331753	904346
25-49	5704259	3416411	9120670
50-59	10858865	8242543	19101408
60-69	15491131	8154724	23645855
70-79	9105161	5083560	14188721
80+	1846403	1662903	3509306
Unknown	8265	3932	12197
Others[b]	8501218	5851978	14353196
Total	**67013388**	**38402180**	**105415568**

[a] Administration data for the European Union, United Kingdom and Australia is available on a weekly basis. 27 June 2021 was the closest available distribution data to the data-lock point of this PBRER (28 June 2021).

[b] "Others" includes administration data where vaccinee age is reported as "adult" or as another non-specific age description

The total doses administered by Age group does not reflect the total doses administered that appears in Table 6. This is due to the fact that doses administered by Age group is not available for all countries that have provided vaccine administration information.

COVID-19 Coronavirus Disease 2019.

Table 8 present the vaccine doses administered by Gender Group for the following specific countries:

- Australia and UK

Table 8 COVID-19 VACCINE ASTRAZENECA Cumulative Exposure Based on Doses Administered by Gender from 29 December 2020 through 27 June 2021[a]

Gender group	Total doses administered
	Cumulative
Male	23623400
Female	24960135

Table 8 COVID-19 VACCINE ASTRAZENECA Cumulative Exposure Based on Doses Administered by Gender from 29 December 2020 through 27 June 2021[a]

Gender group	Total doses administered
	Cumulative
Unspecified	184054
Total	**48767589**

[a] Administration data for the European Union, United Kingdom and Australia is available on a weekly basis. 27 June 2021 was the closest available distribution data to the data-lock point of this PBRER (28 June 2021).

The total doses administered by Gender group does not reflect the total doses administered that appears in Table 6. This is due to the fact that doses administered by Gender group is not available for all countries that have provided vaccine administration information.

COVID-19 Coronavirus Disease 2019

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

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 24.0, 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 June 2021 organised by SOC, is presented in Appendix 2.

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

A cumulative summary tabulation 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 DLP, organised by SOC, are presented in Appendix 2.

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

6.3.1.1 Fatal Events

During the reporting period, 2748 fatal cases were received. In 579 of the 2748 case reports, the vaccinees were aged 80 years and above. The mean age of the fatal cases was 67 years. Age was unknown in 368 cases. Important co-morbid conditions reported included dementia, frailty, hypertension, diabetes mellitus, ischemic heart disease, heart failure, atrial fibrillation, valvular heart disease, coronary artery disease, hyperlipidaemia, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, stroke, epilepsy, hypothyroidism, autoimmune disorders, Parkinson's disease, depression, anxiety, malignancies, and substance abuse. The cause of death was not stated in 938 case reports. Due to limited information contained in the reports, cause of death was difficult to ascertain.

Of the remaining 1810 case reports received during the reporting interval the cause of death was cardiorespiratory (616), thrombosis with thrombocytopenia (89) including 25 cases of cerebral venous sinus thrombosis (CVST) and 7 were cerebral venous thrombosis (CVT) cases. Further causes of death included: TCP (35), thrombosis (340), CVST without thrombocytopenia (39), CVT without thrombocytopenia (15), cerebrovascular accident (204), infection (219), malignancy (8), Multiple organ dysfunction syndrome (18), seizure (7), renal causes (15), brain death/injury (24), fall/accidental (9), physical health deterioration/disease progression (9), anaphylaxis/shock (15), suicide/intentional overdose (6), bleed (16), neonatal (Abortion spontaneous, stillbirth, premature rupture of membranes, neural tube defect) (5), gastrointestinal causes (17), and other (104). Of the 219 case reports where infections were reported as the cause of death, 121 reported COVID-19 infection as the cause of death. Of these 121 cases, 112 were reported after a single dose of the vaccine (time to onset ranged from the same day as vaccination to 73 days); 9 were reported after 2 doses of the vaccine (time to onset ranged from 6 days after vaccination to 67 days). Other infections were sepsis (28), pneumonia (49), influenza (5), lower respiratory tract infection (5), meningitis (1), osteomyelitis (1), UTI (1), encephalitis (1), cellulitis (1), and not reported (5).

Of the 2748 fatal case reports during this reporting period, 1550 were medically confirmed and 1198 were non medically confirmed. Of the 2748 cases, 152 were reported as Sudden Death. See Section 6.3.1.2, for a detailed review of cases of Sudden death..

Table 9 presents an overview of fatal cases per age group during the reporting period.

Table 9 Fatal cases per age group (in years)

Age group	Fatal cases
< 18	3
18-49	353
50-59	324
60-64	287
65-74	571
≥ 75	842
Unknown	368
Total	**2748**

An O/E analyses for fatal cases was completed and the results of the O/E analyses are presented in Table 10. References for background estimates obtained from the literature are provided in Appendix 9.

Table 10 Observed versus expected analyses for All Fatal cases and Fatal cases by age group in EU/UK

Medical Concept	Age Group	Observed cases	Expected cases	Rate ratio (CI 95%)	
Fatal Reports [a] (from EU and UK)	18 - 49	277	1115.58	0.25 (0.22 - 0.28)	Observed significantly < expected
	50 - 59	227	6615.79	0.03 (0.03 - 0.04)	Observed significantly < expected
	60 - 69	427	19202.65	0.02 (0.02 - 0.02)	Observed significantly < expected
	70 - 79	427	26353.23	0.02 (0.01 - 0.02)	Observed significantly < expected
	>80	459	34652.86	0.01 (0.01 - 0.01)	Observed significantly < expected
Overall [b]		2781	110399.96	0.03 (0.02 - 0.03)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from EU and UK, as corresponding exposure was only available from these regions.

[b] Global reports, includes 2716 processed cases and 65 unprocessed cases up to 28 June 2021 regardless of time to onset.

CI Confidence Interval; EU European Union; UK United Kingdom.

As illustrated in Table 10 above, the observed number of fatal cases was significantly less than expected overall and for all age groups examined.

As per the information obtained from the MHRA website, a high proportion of people vaccinated early in the vaccination campaign so far in the UK are very elderly, many of whom likely have pre-existing conditions. Older age and chronic underlying illnesses make it more likely that coincidental adverse events will occur (MHRA 2021).

AstraZeneca will continue to closely monitor fatal outcomes and will inform on unusual trends or patterns to global regulatory authorities without delay.

6.3.1.2 Events with PT of Sudden Death

During the reporting period, 139 cases containing the PT of Sudden death, 12 cases containing the PT of Sudden cardiac death, and 1 case containing the PT Sudden unexplained death in epilepsy.

Of the 152 case reports with Sudden death outcome, 120 were medically confirmed and 32 were non-medically confirmed. Sixty-four vaccinees were female, 87 were male, and 1 vaccinee was of unknown gender. Age of vaccinees ranged from 20 to 97 years with a mean age of 67 years. The medical history (vaccinees may have had >1 comorbidity) included COPD, hypertension, diabetes mellitus, schizophrenia, alcoholic cirrhosis, arterial occlusive disease, cardiac disorder, 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. For 41 vaccinees, the medical history was not reported.

There were 146 cases where time to death ranged from the same day as vaccination to 81 days after receiving the first dose of the vaccine. There were 6 cases where time to death was: the same day as vaccination, 1 day, 3 days, 7 days, 81 days, and unknown number of days after receiving the second dose.

Time to death was unknown for 21 cases. Of the 152 cases of sudden death, cause of death, as stated in reports, was provided in 46 cases and included PTs of Cardiac arrest, Myocardial ischaemia, Left ventricular dysfunction, Atrial fibrillation, Pneumonia, Pulmonary embolism, Asthenia, Hyperpyrexia, Arthralgia, Cardio-respiratory arrest, Chest pain, Deep vein thrombosis, Subarachnoid haemorrhage, Aneurysm ruptured, Contusion, Cardiomegaly, Myocardial infarction, Acute coronary syndrome, Cardiovascular disorder, Visceral venous thrombosis, Cor pulmonale acute, Respiratory arrest, Hypertension, Haemorrhage intracranial, Dyspnoea, Cardiac fibrillation, Cerebral infarction, Gastrointestinal haemorrhage, Acute

myocardial infarction, Cerebrovascular accident, Cardiac failure chronic, Coronary artery occlusion, and Circulatory collapse.

This review of cases of all fatal case reports and a specific review of Sudden death did not indicate any pattern or cluster suggesting a potential safety concern.

6.3.2 Post-marketing reports of Lack of efficacy

During the reporting period, using the Lack of Efficacy Standardised MedDRA Query (SMQ), 635 reports were identified, which involved 641 Lack of Effect AEs: Drug ineffective (517), Vaccination failure (72), Therapeutic product ineffective (18), Treatment failure (7), Disease progression (7), Therapeutic product effect decreased (4), Therapy non-responder (2), Therapeutic response shortened (2), Therapeutic product effect delayed (2), Paradoxical drug reaction (2), Therapeutic product effect incomplete (1), Remission not achieved (1), Device defective (1), Drug level decreased (1), Diet failure (1), Therapeutic reaction time decreased (1), Therapeutic response decreased (1), Drug effect less than expected (1).

Of the 635 reports, 179 were medically confirmed and 466 non-medically confirmed. A total of 234 reports were serious and 401 were non-serious. There were 11 fatal cases in the reporting period. Further details of these fatal cases are presented in Table 9.

Table 11 Summary of fatal Lack of Efficacy (n = 11) with COVID-19 VACCINE ASTRAZENECA reported during the reporting period (29 December 2021 to 28 June 2021)

Case ID	Case details
PPD	A vaccinee from PPD experienced COVID-19 positive 49 days after receiving the second dose (PT: Vaccination failure). The vaccinee's health worsened and was put on ventilator. The vaccinee died 20 days after experiencing COVID-19 positive. It is not known whether an autopsy was performed
PPD	A PPD-year-old vaccinee from PPD with multiple comorbidities died on an unknown date after vaccination. Cause of death was listed as disease progression on an unknown date (PT: Disease progression). It is not known whether an autopsy was performed.
PPD	A PPD-year-old vaccinee from the PPD died on an unknown date after receiving the second dose. Autopsy was not performed. The cause of death was lack of efficacy (PT: Drug ineffective).
PPD	A vaccinee from the PPD experienced acute coronary syndrome, tachycardia, body malaise, chest pain, shortness of breath and difficulty on breathing on ascending PPD 2 days after vaccination. On an unknown date, the patient experienced COVID-19 suspect (PT: Therapeutic product ineffective). The vaccinee died on an unspecified date (cause of death: acute coronary syndrome, tachycardia, body malaise, chest pain, shortness of breath, difficulty on breathing on ascending the stairs and covid-19 suspect). It is not known whether an autopsy was performed.

Table 11 Summary of fatal Lack of Efficacy (n = 11) with COVID-19 VACCINE ASTRAZENECA reported during the reporting period (29 December 2021 to 28 June 2021)

Case ID	Case details
PPD	A vaccinee from PPD experienced COVID-19 pneumonia the same month as vaccination (PT: Vaccination failure). Twenty-four days after vaccination, the vaccinee experienced a stroke on the same day and subsequently died on an unknown date. It is not known whether an autopsy was performed. The cause of death was middle cerebral artery occlusion and COVID-19 pneumonia.
PPD	A vaccinee from the PPD died 89 days after receiving the 2nd dose (PT: Drug ineffective). It is not known whether an autopsy was performed. The cause of death was unknown.
PPD	A vaccinee from PPD experienced COVID-19 (PT: Vaccination failure) and died due to COVID-19 pneumonia about 2 months after receiving the 2nd dose.
PPD	A vaccinee from PPD experienced COVID-19 symptoms one day after vaccination and hemispheric stroke on an unspecified date. This vaccinee had a positive COVID-19 test (PT: Drug ineffective) on an unspecified date. The vaccinee died on an unspecified date (cause of death: Cerebrovascular accident). It is not known whether an autopsy was performed.
PPD	A PPD-year-old vaccinee from PPD experienced COVID-19 (PT: Drug ineffective) 7 days after vaccination and died 3 days later from the event of positive COVID-19 and lack of efficacy. An autopsy was performed. The cause of death was positive COVID-19 (confirmed at autopsy) and lack of efficacy.
PPD	A vaccinee from PPD experienced events of Respiratory failure, SARS-CoV-2 test positive (PT: Drug ineffective), Hypoventilation, and Pyrexia on unknown dates. The cause of death was unknown.
PPD	A vaccinee from PPD experienced pneumonia and a positive COVID-19 test (PT: Drug ineffective) 3 days after vaccination. The vaccinee died 3 days after vaccination (cause of death: pneumonia).

COVID-19 Coronavirus Disease 2019, PT Preferred Term, SARS-CoV-2 Severe Acute Respiratory Coronavirus 2.

Of the 624 non-fatal cases, outcomes were as follows: Not recovered (171), Recovered (149), Recovered with sequelae (2), Recovering (71), and Unknown (231).

Information on COVID-19 test was available in 186 reports; of these 105 were reported as COVID-19 test positive and 81 were reported as COVID-19 test negative. Information on the 105 reports with a positive COVID-19 test is presented below:

- In 87 of the 105 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 64 cases and ranged from the same day as vaccination to 77 days [same day (1), 2 days (7), 3 days (1), 4 days (1), 6 days (1), 7 days (2), 10 days (1), 11 days (3), 12 days (1), 13 days (1), 14

days (2), 15 days (2), 16 days (3), 17 days (3), 19 days (2), 20 days (1), 22 days (1), 24 days (1), 25 days (2), 26 days (2), 28 days (1), 29 days (3), 30 days (1), 32 days (2), 33 days (1), 36 days (1), 37 days (2), 39 days (1), 41 days (1), 42 days (2), 43 days (2), 44 days (1), 52 days (2), 53 days (1), 58 days (1), 62 days (1), 65 days (1), 69 days (1), and 77 days (1)]. In 23 reports, time to positive COVID-19 test after first dose of vaccine was unknown. In 6 reports, positive COVID-19 test was 67 days, 133 days, 139 days, 161 days, 169 days, and 293 days prior to the first dose of vaccine.

- In 12 reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; the time intervals were the same day, 15 days, 17 days, 19 days, 21 days, 25 days, 28 days, 33 days, 36 days, 38 days, 45 days, and 76 days after second dose.

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

7.1 Completed clinical trials

No clinical trials have completed during the reporting period.

7.2 Ongoing clinical trials

There were 10 (COV001, COV002, C0V003, COV004, COV005, COV006, COV008, D8110C0001, D8111C00002 and D7220C00001) ongoing clinical trials during the reporting period. For the D8110C0001 study as well as COV001, COV002, COV003 and COV005 studies enrolment had completed at the time of the primary analyses.

There was no additionally 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

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 a 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 x1010 vp) and/or the standard dose (SD) (~5x1010 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 a 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 (~2.5x1010 vp) and/or the SD (~5x1010 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 a 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 SARSCoV- 2 virus. Participants are randomised to receive either a 2-dose regimen of the SD (~5x1010 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 a phase Ib/II trial single-blinded, randomised, controlled study of the SD (~5x1010 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 (~5x1010 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 (~5x1010 vp) of COVID-19 VACCINE ASTRAZENECA or rabies vaccine will be distributed 1 month apart. 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 a 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 x1010 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.

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 a Phase II, single-blinded, active-controlled, randomised study in approximately 300 healthy children and adolescents aged 6-17 years in the UK, 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 (~5x1010 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 a Phase I, open label, dose escalation study in up to 54 healthy adults aged 18-40 years in the UK. The study will investigate safety, tolerability and immunogenicity of one or two doses of intranasal ChAdOx1 nCOV-19 (5x109 vp, 2x1010 vp or 5x1010 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.

Efficacy, safety, and immunogenicity results from pooled analyses including data from COV001, 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. The vaccine was well tolerated in pooled safety analyses.

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 a 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. 32451 participants were randomised in a 2:1 ratio to receive 2 IM doses of either the SD (~5x1010 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

At the data cut-off of 05 March 2021, the primary efficacy analysis included the accrual of 190 symptomatic cases of COVID-19 from the 26406 study participants who were seronegative at baseline, received 2 doses of study intervention (4 weeks apart), and were followed for ≥ 15 days post second dose without having a prior SARS-CoV-2 Real-Time polymerase chain reaction (RT-PCR) confirmed infection Fully Vaccinated Analysis Set (FVS). The primary endpoint of VE at preventing symptomatic COVID-19 illness was 76.0% (95% CI: 67.6%, 82.2%). An updated primary efficacy analysis included the accrual of 203 symptomatic cases of COVID-19 from the 26212 study participants who were seronegative at baseline, received 2 doses of study intervention (4 weeks apart), and were followed for ≥ 15 days post second dose without having a prior SARS-CoV-2 RT-PCR confirmed infection FVS. The updated primary endpoint of VE at preventing symptomatic COVID-19 illness was 74.0% (95% CI: 65.3%, 80.5%). In addition, results were comparable across age groups, with VE of 72.8% (95% CI: 63.4%, 79.9%) in adults ≥ 18 to < 65 years and 83.5% (95% CI: 54.2%, 94.1%) in adults ≥ 65 years of age. A key secondary endpoint, preventing severe or critical disease, demonstrated 100% efficacy. There were 8 cases of severe COVID-19 in the primary analysis with all of those cases occurring in the placebo group. Vaccination with VAXZEVRIA was well tolerated in this study. The incidence of SAEs was low (< 1%) in both the VAXZEVRIA and placebo groups, with no difference in either frequency or type of SAEs between the treatment groups. No death was considered related to VAXZEVRIA by the Investigator.

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 a 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 VAXZEVRIA with 5x1010 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 VAXZEVRIA 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, VAXZEVRIA elicited strong humoral immune responses against SARS-CoV-2 (anti-Spike and anti- receptor-binding domain (RBD)

antibodies and neutralising antibody) regardless of age. VAXZEVRIA was well tolerated, 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 a 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 2250 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 1200 previously vaccinated participants receiving single-dose vaccination and 1050 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 ×1010 vp) or AZD2816 (5 ×1010 vp). Dosing intervals will be 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.

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 10 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. COVID-19 VACCINE ASTRAZENECA has been shown to be safe and well tolerated. The occurrence of very rare thromboembolic events with TCP identified during post-market approval led to the re-assessment of COVID-19 VACCINE ASTRAZENECA benefit-risk balance, which remains positive.

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.

7.4 Other therapeutic use of medicinal product

There were no other AstraZeneca programmes that follow a specific protocol with solicited reporting for COVID-19 VACCINE ASTRAZENECA.

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

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 errors 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 medication errors included the following PTs;

- PTs in the SMQ Medication errors and
- PTs: 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.

A total of 3264 case reports, including 3732 medication error AEs, have been identified during the reporting period. Of those, 3732 events 221 were considered serious. Of the 3264 case reports, 1765 case reports were medically confirmed and 1499 were non-medically confirmed. In 2131 of the 3264 case reports no other AEs were reported in connection with the medication error. AE's were reported in the remaining 1133 case reports.

Out of the 1133 cases with adverse events, 392 (34.6%) cases were serious and 741 (65.4%) were non-serious. Of the 1133 cases, 242 (21.4%) were medically confirmed and 891 (78.6%) were non-medically confirmed. 7 cases were associated with fatal outcome. Out of 392 cases, the seriousness criteria were fatal/death in 7 case reports, hospitalisations in 83 cases and the remaining were medically important.

Summary of the two fatal cases associated with vaccination error are described below:

PPD **:** A case report of a PPD patient of unknown ethnic origin (age PPD years, height PPD cm, weight PPD kg) consumer. The patient's past and current medical history included PPD (dates not reported). Concomitant medication included PPD On PPD, the patient received COVID-19 VACCINE ASTRAZENECA (chadox1 ncov-19) (batch number ABU8139), IM. On the same day, the patient experienced allergic reaction, severe vomiting, severe stopping blood circulation, PPD, breathing problems, severe increasing shortness of breath, severe loss of consciousness, PPD. In addition, subcutaneous route of administration (actual medication error) was also mentioned. It was reported that on PPD, the patient died from the event of allergic reaction, vomiting, stopping blood circulation, PPD, breathing problems, increasing shortness of breath, loss of consciousness and PPD. The cause of death was central cyanosis, breathing problems, allergic reaction, increasing shortness of breath, vomiting, loss of consciousness, stopping blood circulation and blue face and neck.

PPD **:** A case report of a PPD-year-old PPD patient of PPD ethnic origin (height: PPD in). Patient's past and current medical history included PPD (dates not reported) and PPD (dates not reported). No concomitant products were reported. On an unknown date, the patient received COVID-19 VACCINE ASTRAZENECA (covid-19 vaccine nrvv ad (chadox1 ncov-19) (batch number unknown), via IM route for covid vaccine. The report described a medication error for COVID-19 VACCINE ASTRAZENECA and the reported term was route of administration: intravenous (actual medication error). On PPD, the patient died due to blood clotting in the brain. On an unknown date, the patient experienced rupture of vein in the brain, severe headache for 5 days before death, detection of mild COVID-19 in the lungs X-ray. The reporter stated the medication error info:

Actual medication error with harm, Stage: Administration, Medication error with AE, Circumstances: route of administration is reported as intravenous. Treatment with COVID-19 VACCINE ASTRAZENECA (COVID-19 vaccine nrvv ad (chadox1 ncov-19)) was not changed. The patient died due to blood clotting in the brain, intravenous route of administration, Vein rupture in brain, severe headache for 5 days and mild COVID-19 in the lungs X-ray. Autopsy not performed and the cause of death was blood clotting in the brain, IV route of administration, vein rupture in brain, severe headache and mild COVID-19.

Out of 1133 case reports there were 5822 events (1682 serious and 4144 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 12).

Table 12 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 June 2021

MedDRA (SOC)	Events Count	Percentage
General disorders and administration site conditions	**1755**	**30.14**
Injury, poisoning and procedural complications	1244	21.36
Nervous system disorders	811	13.93
Musculoskeletal and connective tissue disorders	528	9.07
Gastrointestinal disorders	296	5.08
Skin and subcutaneous tissue disorders	164	2.82
Investigations	148	2.54
Respiratory, thoracic and mediastinal disorders	147	2.52
Infections and infestations	119	2.04
Psychiatric disorders	101	1.73
Vascular disorders	82	1.41
Eye disorders	71	1.22
Surgical and medical procedure	68	1.17
Cardiac disorders	46	0.79
Metabolism and nutrition disorders	44	0.76
Ear and labyrinth disorders	38	0.65
Blood and lymphatic system disorders	32	0.55
Reproductive system and breast disorders	32	0.55
Immune system disorders	22	0.38
Product issues	22	0.38
Social circumstances	16	0.27
Renal and urinary disorders	15	0.26

Table 12 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 June 2021

MedDRA (SOC)	Events Count	Percentage
General disorders and administration site conditions	**1755**	**30.14**
Pregnancy, puerperium and perinatal conditions	11	0.19
Hepatobiliary disorders	5	0.09
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	0.05
Congenital, familial and genetic disorders	1	0.02
Endocrine disorders	1	0.02

COVID-19 Coronavirus Disease 2019, MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class.

Most frequently reported AEs ≥ 50 within the 1133 case reports of vaccination error were Pyrexia (393), Headache (357), Chills (265), Fatigue (187), Pain (171), Pain in extremity (141), Myalgia (133), Malaise (107), Dizziness (99), Arthralgia (98), Nausea (95), Injection site pain (93), Asthenia (89), Vomiting (51), all of which were listed.

The reported medication error AEs are presented in Table 13.

Table 13 AZD1222 - Summary tabulation of Medication Error Adverse Events

Adverse Event (MedDRA PT)	Cumulative			
	With AE		Without AE	
	Serious	Non-Serious	Serious	Non-Serious
Accidental exposure to product	10	4	0	5
Accidental overdose	2	5	1	13
Accidental underdose	1	5	0	11
Booster dose missed	0	0	0	3
Circumstance or information capable of leading to device use error	0	0	0	1
Circumstance or information capable of leading to medication error	3	20	0	48
Contraindicated product administered	3	1	0	1
Contraindicated product prescribed	8	1	0	0
Contraindication to medical treatment	0	1	0	0
Contraindication to vaccination	4	0	0	0
Device connection issue	0	0	0	2

Table 13 AZD1222 - Summary tabulation of Medication Error Adverse Events

Adverse Event (MedDRA PT)	Cumulative			
	With AE		Without AE	
	Serious	Non-Serious	Serious	Non-Serious
Device maintenance issue	0	0	0	1
Device use confusion	0	1	0	0
Device use error	0	0	0	1
Device use issue	1	0	0	0
Documented hypersensitivity to administered product	0	0	0	2
Dose calculation error	0	4	0	0
Drug monitoring procedure not performed	0	0	0	1
Duplicate therapy error	0	0	0	1
Expired product administered	21	15	0	14
Exposure to contaminated device	1	0	0	0
Exposure via partner	1	0	0	0
Exposure via unknown route	0	1	0	0
Extra dose administered	1	4	0	34
Inadequate aseptic technique in use of product	1	1	0	0
Inappropriate schedule of product administration	2	119	1	201
Incomplete course of vaccination	1	14	0	15
Incorrect dosage administered	0	2	0	18
Incorrect dose administered	6	53	0	133
Incorrect product administration duration	0	1	0	8
Incorrect product formulation administered	0	0	0	1
Incorrect route of product administration	22	260	0	19
Injury associated with device	8	6	0	0
Intercepted accidental exposure to product by child	0	0	0	1
Intercepted medication error	0	4	0	239
Intercepted product administration error	1	4	0	7
Intercepted product preparation error	0	0	0	2

Table 13 AZD1222 - Summary tabulation of Medication Error Adverse Events

Adverse Event (MedDRA PT)	Cumulative			
	With AE		Without AE	
	Serious	Non-Serious	Serious	Non-Serious
Intercepted product storage error	0	1	0	186
Interchange of vaccine products	4	39	0	40
Lack of vaccination site rotation	1	0	0	0
Medical device monitoring error	0	0	0	1
Medication error	26	210	2	560
Multiple use of single-use product	0	0	0	1
Needle issue	1	5	1	6
Occupational exposure to product	4	4	0	5
Overdose	22	15	0	35
Poor quality product administered	0	0	1	13
Prescribed overdose	0	1	0	0
Prescribed underdose	0	3	0	0
Prescription drug used without a prescription	3	0	0	0
Product administered at inappropriate site	11	28	0	7
Product administered to patient of inappropriate age	2	33	1	42
Product administration error	7	27	0	60
Product barcode issue	1	0	0	0
Product communication issue	0	2	0	3
Product dispensing error	10	5	0	5
Product dispensing issue	0	0	0	1
Product dose omission in error	1	4	0	7
Product dose omission issue	2	33	0	34
Product identification number issue	0	0	0	2
Product label confusion	0	1	0	2
Product label issue	0	2	0	1
Product lot number issue	0	0	0	5
Product monitoring error	1	0	0	1
Product name confusion	1	1	0	0

Table 13 AZD1222 - Summary tabulation of Medication Error Adverse Events

Adverse Event (MedDRA PT)	Cumulative			
	With AE		Without AE	
	Serious	Non-Serious	Serious	Non-Serious
Product preparation error	0	0	0	1
Product preparation issue	0	0	0	2
Product prescribing error	1	6	0	10
Product prescribing issue	0	1	0	2
Product selection error	0	0	0	2
Product storage error	0	29	0	336
Product substitution error	0	0	0	1
Product temperature excursion issue	0	4	0	289
Product use in unapproved indication	1	1	0	0
Product use issue	4	9	0	6
Syringe issue	0	3	0	9
Transcription medication error	0	3	0	0
Underdose	1	12	2	118
Unintentional use for unapproved indication	0	0	0	1
Vaccination error	4	7	0	28
Wrong device used	0	2	0	0
Wrong dose	0	1	0	0
Wrong drug	0	0	0	4
Wrong patient received product	0	1	0	0
Wrong product administered	2	8	0	16
Wrong route	0	2	0	0
Wrong schedule	0	2	0	14
Wrong technique in device usage process	0	2	0	0
Wrong technique in product usage process	4	6	1	7
Grand Total	**211**	**1039**	**10**	**2645**

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.

Case reports may include more than one medication error AE.

AE Adverse Event, MedDRA Medical Dictionary for Regulatory Activities , PT Preferred term.

Summary and Conclusion

The most frequently reported PTs during the reporting period were Medication error (786), Product storage error (373), Inappropriate schedule of product administration (309), Product temperature excursion issue (299), Incorrect route of product administration (299), Intercepted medication error (249), Intercepted product storage error (183), Incorrect dose administered (183), Underdose (130), Product administration error (95).

In the reporting interval there were 301 cases reported for PT 'Incorrect route of product administration. Of these 65 were subcutaneous, 29 were intravenous, 6 were intradermal, 5 were oral, 3 were cutaneous, 1 was inhalational, 1 was subconjunctival, 1 was intra-articular, 1 was parenteral and 1 nasal. All of the co-reported adverse events with the vaccination error(s) were listed

AstraZeneca comment: No new relevant patterns of medication errors or potential medication errors were identified during the PBRER reporting period.

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.

AstraZeneca has reviewed the published non-clinical scientific literature relevant to COVID-19 VACCINE ASTRAZENECA. No publications were identified that included any relevant safety information or information with potential impact on the benefit or risk evaluations 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 AstraZeneca COVID-19 vaccine 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. The findings from these articles are summarized below. As applicable, additional articles of interest related to Important Identified and Potential risks or missing information have been included within the review of those safety concerns throughout Section 16.

Bleeding events/Haemorrhages after COVID-19 Vaccination

Simpson et al investigated associations between haematological and vascular AEs after a single dose of the COVID-19 VACCINE ASTRAZENECA or BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines (Simpson et al 2021). The study was based on a national prospective COVID-19 surveillance cohort in Scotland covering 5.4 million people (~99% of the Scottish population) and included data from 2.53 million people who received first doses of COVID-19 vaccines in Scotland between 08 December 2020 and 14 April 2021. Of these, 1.71 million people were vaccinated with COVID-19 VACCINE ASTRAZENECA. The authors carried out an analysis of observed incident cases in the post-vaccination period compared with those expected from a pre-vaccination period. The pre-vaccination period was the 28-day period after 01 October 2020. For the event to be incident, no thrombocytopenic, venous thromboembolic, or haemorrhagic events could have occurred in the same individual in the period from 01 September 2019. The expected events were the number of events per day in the pre-vaccination period divided by the population and multiplied by the days at risk in the post-vaccination period for all vaccinated and then summed. The difference between expected and observed events during the post-vaccination period was used to calculate expected additional cases per 100000 vaccine doses. Details on the demography or baseline characteristics of the vaccinated population were not provided except for age. The authors note that the proportion of vaccinated people < 40 years was low, especially for COVID-19 VACCINE ASTRAZENECA, and that the vaccination programme has been predominantly targeted by age and comorbidities during the reported period. The authors concluded that there may be a small increased risk of ITP following first dose of COVID-19 VACCINE ASTRAZENECA.

AstraZeneca Comment: There was evidence of an increased risk of thrombocytopenic events 0 to 6 days after first dose of COVID-19 VACCINE ASTRAZENECA but not during the period 0 to 27 days after first dose. The risk of idiopathic thrombocytopenic purpura was increased with COVID-19 VACCINE ASTRAZENECA (adjusted rate ratio of 5.77 [95% CI: 2.41 to 13.83] 0 to 27 days after first vaccination). No increased risk of venous thromboembolic events was identified for COVID-19 VACCINE ASTRAZENECA; however, the study was not powered to detect differences in CVST.

The study by Trogstad et al 2021 compared skin, nose, and gingival bleeding rates following receipt of a single dose of a Messenger Ribonucleic Acid (mRNA) vaccine (ie, BNT162b2 and COVID-19 Vaccine Moderna) or adenoviral vaccine (ie, COVID-19 VACCINE ASTRAZENECA) against COVID-19 (Trogstad et al 2021). The study was based on questionnaires provided on 17 March to adult participants in the Norwegian Mother, Father and Child Cohort Study. In total, 81267 of 138924 people responded to the questionnaire (response rate of 58%), of whom 8699 (11%) reported receiving either an mRNA or adenoviral vaccine. No responders had received 2 doses of an adenoviral vaccine; 3135

responders had received 2 doses of an mRNA vaccine. The majority (≥ 80%) of responders who had received vaccines were healthcare workers, women, and aged 25 to 49 years. Bleeding episodes of the skin (bruising/skin bleeding) were significantly more frequent among recipients of the first dose of adenovirus vectored vaccine (3.2%) as compared to the first dose of the mRNA vaccines (0.2%), corresponding to an odds ratio of 16.0 (95% CI: 7.5 – 34.1). Similar, but lower associations were found for nose and gingival bleedings.

AstraZeneca Comment: Based on the design of the study and the small sample size, the potential for reporting bias in this study is large.

Capillary Leak Syndrome

Case reports of exacerbation of capillary leak syndrome following COVID-19 vaccination have been reported in the literature Matheny et al 2021 presented a case series involving 3 patients with history of systemic capillary leak syndrome (SCLS) who had severe flairs following COVID-19 vaccination. Two of the patients developed SCLS after their second doses of mRNA vaccines (Moderna and Pfizer) or a single dose of adenoviral vector vaccine (Johnson & Johnson – Janssen) vaccine. All patients developed life-threatening flairs 1 – 2 days after vaccination, with a fatal outcome reported in 1 patient. The authors note that these patients may indicate a serious adverse reaction following COVID-19 vaccination, but these observations do not rule out other causes, including infectious causes, such as COVID-19. Robichaud et al 2021 presented a case report of a PPD patient who developed acute exacerbation of SCLS two days after receiving PPD first dose of COVID-19 VACCINE ASTRAZENECA.

AstraZeneca Comment: Since publication of these and other case reports of exacerbation of capillary leak syndrome following vaccination with adenoviral vector vaccines, several global health authorities, including EMA, have imposed contraindicated the use of these COVID-19 vaccines in patients with medical history of capillary leak syndrome. ASTRAZENECA maintains there is insufficient evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and emergent CLS. AstraZeneca continues to closely monitor cases of CLS as part of routine surveillance activities.

Effectiveness of COVID-19 VACCINE ASTRAZENECA Against SARS-COV-2 Variants

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of SARS-CoV-2 variants, B.1.1.7 (alfa) in the UK, B.1.351 (beta) in South Africa, and P.1 (gama) in Brazil. These variants carry mutations in the S protein sequence: 9 in B.1.1.7, 10 in B.1.351, and 12 in P.1 compared with the Wuhan sequence. These mutations may result in an increase of transmissibility (Volz et al 2021, Davies et al 2021, Pearson et al 2021) and the vaccine may not be as effective against these variants (Wang et al 2021a, Muik

et al 2021, Wu et al 2021, Madhi et al 2021). A key issue is whether COVID-19 vaccines, including COVID-19 VACCINE ASTRAZENECA, will be able to protect against infection or disease from the emerging new SARS-CoV-2 variants. An interim analysis of Study COV005 conducted in South Africa showed limited VE of 10.4% (95% CI, −76.8 to 54.8) against the SARS-CoV-2 B.1.351 (beta) variant (Madhi et al 2021). However, a post-hoc analysis of Study COV002 (UK) showed that COVID-19 VACCINE ASTRAZENECA was efficacious against B.1.1.7 variant, yielding VE of 70.4%, with a lower bound of 43.6% for the 95% CI (Emary et al 2021).

A new variant of concern, B.1.617.2 (delta), initially identified in India in May 2021, has become dominant in the UK. A recent linkage healthcare data set study conducted in the UK, reported COVID-19 VACCINE ASTRAZENECA yielded vaccine effectiveness against hospitalisation of 71% after a single dose and 92% after 2 doses among over 14,000 patients who tested positive with the B.1.617.2 variant, indicating that COVID-19 VACCINE ASTRAZENECA remains effective against the most prevalent emergent variant dominant in the UK (Stowe J.et al).

AstraZeneca is currently developing an updated COVID-19 VACCINE ASTRAZENECA vaccine, AZD2816, expected to have efficacy against the B.1.351 (beta) variant.

Guillain-Barre Syndrome After COVID-19 Vaccination

GBS after receiving COVID-19 vaccine has not been reported until 02 February 2021, when the first reported case of GBS after receiving the first dose of Pfizer COVID-19 vaccine was reported in an PPD -year-old highly functional PPD at baseline without significant comorbidities. The authors of this article concluded that the risk of neurological complications or any other adverse effects associated with COVID-19 vaccination is low and the benefits of the vaccination outweigh any potential risks or side effects, both at the individual and society levels (Waheed et al 2021).

Two patients in the Johnson & Johnson COVID-19 vaccine trial developed GBS 10 days after injection; one was in the placebo arm and one was in the active vaccine arm: the incidence of GBS was identical in both arms of the trial. The patient in the vaccine arm did not have any clinical features differentiating PPD from patients with typical GBS.

AstraZeneca Comment: From the available evidence, included in this article, it was not possible to draw a causal inference about the association of COVID-19 vaccination and the development of GBS (Márquez Loza et al 2021).

Myocarditis and Pericarditis After COVID-19 Vaccination

Cases of myocarditis and pericarditis have been reported after administration of mRNA vaccines for COVID-19, including Moderna and Pfizer vaccines (Abu Mouch et al 2021, Wise J 2021, Montgomery et al 2021, Kim et al 2021, Albert et al 2021). Limited case reports of myocarditis and pericarditis following vaccination with adenovirus viral vaccines, including AstraZeneca and Johnson & Johnson - Janssen vaccines have also been reported (Chamling B et al 2021, Pepe S et al 2021). Based on the available data, reports of myocarditis and pericarditis after COVID-19 vaccinations are rare; definitive evaluation of the incidence will be possible in post-marketing studies using large databases (Shay et al 2021).

AstraZeneca Comment: To date, AstraZeneca has not found evidence of a causal relationship between myocarditis or pericarditis and COVID-19 VACCINE ASTRAZENECA. This topic remains under close monitoring as part of AstraZeneca's ongoing surveillance efforts.

Thrombocytopenia after COVID-19 Vaccination

Tarawneh et al 2021 described the case of a PPD-year-old patient who received the Pfizer-BioNTech BNT16B2b2 mRNA vaccine. Three days later, the patient developed immune TCP. The authors attributed the patient's immune TCP was attributed to the vaccination as other possible causes were ruled out.

Toom et al 2021 described a PPD-year-old PPD who was vaccinated with the Moderna COVID-19 vaccine. PPD had a history of PPD This patient developed TCP, manifesting initially as diffuse petechiae, two weeks after vaccination. PPD was treated with steroids and the authors concluded that the vaccination may have triggered the recurring TCP.

Lee et al 2021 included a review of 20 cases of TCP in subjects who received either the Pfizer or Moderna COVID-19 vaccines. Nine patients received the Pfizer vaccine and 11 received the Moderna COVID-19 vaccine. The authors concluded that the event of TCP was similar in frequency to the expected background rate of immune TCP, especially considering that 17 million doses of the vaccines had been administered at the time of review.

Greinacher et al 2021 reviewed 9 patients who experienced thrombotic events and/or TCP after vaccination with COVID-19 VACCINE ASTRAZENECA to determine if the patients could have a prothrombotic disorder caused by platelet-activating antibodies directed against platelet factor 4 (PF-4). The 9 patients (8 females; median age 36 [range, 22-49]) presented with thrombosis 4–16 days post-vaccination. Seven patients had CVST, 1 had pulmonary embolism (PE), and 1 had splanchnic vein thrombosis and CVST. Four patients died, of which all 4 tested strongly positive for anti-PF-4/heparin antibodies by immunoassay and in the

platelet activation assay in the presence of PF-4 independently of heparin. Platelet activation was inhibited by high concentrations of heparin, Fc receptor blocking monoclonal antibodies, and intravenous immunoglobulin (IVIG). This study could not distinguish whether the antibodies were autoantibodies against PF-4 induced by the inflammatory stimulus of vaccination or if the vaccine itself triggered the formation of platelet activating antibodies. The authors advised that sera reactivity in the presence of COVID-19 VACCINE ASTRAZENECA could be explained by direct binding of the virus to platelets, as the authors noted adenoviruses can bind to platelets and cause pre-activation.

A safety report published by Paul-Ehrlich-Institut summarises reports of suspected side effects in Germany following vaccination with any of the approved COVID-19 vaccines (COVID-19 ASTRAZENECA VACCINE, BNT162b2, COVID-19 Vaccine Moderna, and COVID-19 Vaccine Janssen) since the start of the vaccination programme on 27 December 2020 until 31 May 2021 (Paul-Ehrlich-Institut 2021). During the reporting period, approximately 50.5 million doses of COVID-19 vaccines were administered in Germany, of which 9.2 million COVID-19 VACCINE ASTRAZENECA (8.5 million first dose), and a total of 79106 case reports on suspected side effects or vaccination complications after vaccination were registered. Details on the demography or baseline characteristics of the vaccinated population are not provided. TTS was reported following vaccination with COVID-19 VACCINE ASTRAZENECA in 106 cases affecting 70 women (1 of whom had 2 cases of TTS) and 35 men. The age range was 20 to 81 years. All reports except 1 were following the first dose of COVID-19 VACCINE ASTRAZENECA. Of the 105 patients, 31 had cerebral haemorrhages; 20 had thrombosis in multiple organ systems; and 21 died.

AstraZeneca Comment: In AstraZeneca's analyses of TTS, the proportion of women versus men was more similar. The difference in the analysis by Paul-Ehrlich-Institut may be due to the larger proportion of women who had been vaccinated during the reporting period. The age range, fatality rate, and proportion of patients with simultaneous thrombosis at multiple sites were similar to that observed by AstraZeneca. In 43 other cases of sinus vein thrombosis associated with COVID-19 VACCINE ASTRAZENCA, there was no information on platelet count and/or PF4 antibodies or the results of functional coagulation tests, and a causal relationship therefore could not be assessed. Bleeding was reported following vaccination with COVID-19 VACCINE ASTRAZENCA in 650 cases affecting 519 women and 128 men (gender was unknown in 3 cases). The age range was 18 to 95 years. Of the 650 patients, 71 had TCP and 25 died. The report did not include estimates of risk. The process by which the side-effect data was reported into the database and the completeness (eg, extent of missing data) were not described.

Thrombotic Events following COVID-19 Vaccination

The study by Pottegård et al 2021 was a population-based cohort study investigating rates of cardiovascular and haemostatic events after a single dose of COVID-19 VACCINE ASTRAZENECA (Pottegård et al 2021). The study included 0.28 million people aged 18 to 65 years who received a first dose of COVID-19 VACCINE ASTRAZENECA in Denmark and Norway between 09 February 2021 and 11 March 2021. The majority of vaccinees were healthcare and social service workers, and most were female (80.1% women in Denmark; 77.6% women in Norway). A supplementary analysis excluded brief (< 5 hours) hospital contacts to investigate the potential effect of increased diagnostic awareness and thus reporting of less serious events.

Compared with the age-/sex-specific background rates in the respective national populations, there was no increase in arterial events following a first dose of COVID-19 VACCINE ASTRAZENECA, with the exception of intracranial haemorrhage. Venous thromboembolism, including CVST, was increased following a first dose of COVID-19 VACCINE ASTRAZENECA. Slight increases were observed in any TCP /coagulation disorder, with the increase driven by unspecified TCP, and in bleeding.

AstraZeneca Comment: All-cause mortality was reduced following a first dose of COVID-19 VACCINE ASTRAZENECA; the authors suggest that this may be because active healthcare and social services workers (the primary recipients of COVID-19 VACCINE ASTRAZENECA in Denmark and Norway at the time of the study) are likely to be healthier than the average population of the same age. If this is the case, the other results of the study may be similarly confounded, as the expected background rate for some events would be lower in a healthier population.

While the study cohort was smaller than in the other studies discussed and only covered 1 month, the study likely provides the highest-quality data set based on the high quality of the respective registries with full population coverage and the near-complete follow-up.

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

Further analyses to estimate vaccine efficacy of COVID-19 VACCINE ASTRAZENECA against SARS-COV-2 variants of concerns were conducted on data obtained from COOV002 and COV005 trials. An interim analysis of Study COV005 conducted in South Africa showed lower than previously reported VE of 10.4% (95% CI, −76.8 to 54.8) against SARS-CoV-2;

the majority of study participants developed COVID-19 due to the B.1.351 (beta) variant (Madhi et al 2021). For another variant, a post-hoc analysis of Study COV002 (UK) showed that COVID-19 VACCINE ASTRAZENECA was efficacious against B.1.1.7 variant, yielding VE of 70.4%, with a lower bound of 43.6% for the 95% CI (Emary et al 2021). Further information on vaccine efficacy for SARS-CoV-2 variants is described in Section 11 and Section 17.

No data on breakthrough SARS-COV-2 infection were available from ongoing clinical trials. It is anticipated that further data analyses on vaccine efficacy will become available when clinical trials are complete.

14 LATE-BREAKING INFORMATION

In the MSSR PRAC Assessment Report dated 06 July 2021, AstraZeneca was requested, as an imposition, to submit a variation to add a warning about Guillain-Barré Syndrome (GBS) to the COVID 19 VACCINE ASTRAZENECA EU SmPC (Section 16.3.1.1.1).

In response to an imposition from PRAC, the EU RMP was updated post the reporting period to include "Thrombocytopenia with associated bleeding" as an Important potential risk. In addition, during the Late Breaking period, the EU RMP was updated to add AMN/AMOR, PAMM, Paraesthesia and Dysaesthesia as AESIs. Version 4.1 of the EU RMP was submitted to EMA on 12 August 2021. No changes were made to the Core RMP.

15 OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)

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

AstraZeneca are 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 (HCP), 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.

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.

There were 4 validated signals that were either ongoing or closed during the reporting period. The validated signals are provided in Table 14 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 was previously assessed (if applicable).

Table 14 Summary of the validated signals that were ongoing or closed during the reporting period

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)
Hypersensitivity including Anaphylaxis	Closed	Section 16.2.5.1	EMEA/H/C/005675/IAIN/0011
Thrombotic events with Thrombocytopenia	Closed	Section 16.2.3.1	EMEA/H/C/005675/IAIN/0004 and EMEA/H/C/005675/IAIN/0010
Thrombocytopenia	Closed	Section 16.2.5.2	EMEA/H/C/005675/SDA/034
Guillain-Barré Syndrome	Ongoing	N/A	N/A

DLP Data Lock Point, EMA/EMEA European Medicines Agency, N/A Not applicable (signal ongoing), PBRER Periodic Benefit-Risk Evaluation Report.

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:

- Hearing loss (Section 15.2.1)
- Mucocutaneous bleeding (Section 15.2.2)
- Tinnitus (Section 15.2.3)
- Trigeminal neuralgia (Section 16.3.1.1.5)
- Serious hypertension (Section 15.2.4)
- Vertigo (Sections 15.2.5)
- Viral herpes infection (Section 15.2.6)
- Pulmonary Embolism (Section 15.2.7)

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

15.2.1 Hearing Loss

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

The search of the AstraZeneca global safety database identified a cumulative total of 841 processed case reports of hearing loss with COVID-19 VACCINE ASTRAZENECA.

Of the 841 reports of hearing loss, 61.7% of were reported in females and 35% were in males. Gender was not reported in the remaining 3.3% of cases. Age ranged from 18 years to <65 years in 67.3% of the reports, 65+ Years in 21.4% , and 0.24% in less than 18 years of age. Age was not reported in the remaining 12.1% of cases. The majority of reports (86.4%) were not medically confirmed with the remaining 13.6% being medically confirmed.

Of these 841 reports of hearing loss, 689 (81.9%) were considered serious. None of the events had a fatal outcome. Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA to hearing loss was available in 573 of the 841 reports. Most of the events of hearing loss (27.9%) occurred within one day of vaccination, 17.5% occurred 2-5 days post-vaccination, 6.9% occurred between 6-10 days post-vaccination and another 16.8% occurred >10 days after vaccination. Outcome was reported in 717 of the 841 events of hearing loss, with 16.3% reported as Recovered, 15.3% as Recovering, 51.8% Not recovered, and 1.8% as Recovered with sequelae.

Hearing loss often occurred in combination with concomitant contributing events such pyrexia/fever/chills (25.6%), fatigue (14.4%), headache/migraine (28.3%). Moreover, many events were confounded by medical history (ie, suspected COVID-19, cerebrovascular accidents, pre-existing deafness/hearing loss, tinnitus, ear infection, Meniere's disease, labyrinthitis, eustachian tube dysfunction, otitis media, otosclerosis, radiotherapy, meningitis, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and lymphoma; and concomitant medications that may increase the risk of deafness (ie, aspirin, acetylsalicylic acid, azithromycin, furosemide, hydroxychloroquine, quinine, tacrolimus, tadalafil, thyroxine, tetracycline, tadalafil, and ibuprofen).

Due to the broad definition of hearing loss, O/E analysis is not possible for this concept.

Cumulative:

This cumulative 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 is needed at this time. Hearing loss will continue to be monitored as part of AstraZeneca's routine surveillance process.

15.2.2 Mucocutaneous bleeding

As requested by PRAC, a cumulative review of Mucocutaneous Bleeding is presented with a cut-off date of 28 June 2021. The AstraZeneca global safety database was searched using the following MedDRA (v24.0) PTs:

Abnormal uterine bleeding, Anal haemorrhage, Bronchial haemorrhage, Cervix haemorrhage uterine, Conjunctival haemorrhage, Ear haemorrhage, Ecchymosis, Epistaxis, Eye haemorrhage, Gastric haemorrhage, Gastroduodenal haemorrhage, Gastrointestinal haemorrhage, Genital haemorrhage, Gingival bleeding, Haematemesis, Haematochezia, Haematoma, Haematuria, Haemoptysis, Haemorrhage subcutaneous, Haemorrhage urinary tract, Heavy menstrual bleeding, Intermenstrual bleeding, Intestinal haemorrhage, Large intestinal haemorrhage, Laryngeal haemorrhage, Lip haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Menometrorrhagia, Menstruation with increased bleeding, Mouth haemorrhage, Mucocutaneous haemorrhage, Mucosal haemorrhage, Occult blood positive, Oesophageal haemorrhage, Paranasal sinus haemorrhage, Penile haemorrhage, Petechiae, Pharyngeal haemorrhage, Polymenorrhagia, Purpura, Rectal haemorrhage, Respiratory tract haemorrhage, Small intestinal haemorrhage, Tongue haemorrhage, Tonsillar haemorrhage, Tracheal haemorrhage, Ureteric haemorrhage, Urethral haemorrhage, Urinary bladder haemorrhage, Urogenital haemorrhage, Uterine haemorrhage, Vaginal haemorrhage, Vulvar haemorrhage, Upper gastrointestinal haemorrhage, Pulmonary haemorrhage, Pulmonary alveolar haemorrhage.

The search identified a total of 12236 cases. Out of the 12236 cases (13055 events), 9778 cases (80%) were not medically confirmed. There were 5561 (45%) cases that were reported as serious, out of which, 939 were medically confirmed. Of the 12236 cases, 34 cases had 38 adverse events [Gastrointestinal haemorrhage (7), Haematemesis (6), Haemoptysis (5), Epistaxis (4), Gastric haemorrhage (3), Haematoma (2), Melaena (2), Petechiae (2), Rectal haemorrhage (2), Pulmonary haemorrhage (1), Haematuria (1), Mouth haemorrhage (1), Upper gastrointestinal haemorrhage (1), Urinary bladder haemorrhage (1)] reported with fatal outcome.

Out of the 12236 cases, age was reported in 10945 cases, ranging from 16 – 99 years and a median of 48 years. Incorrect age was provided in 12 cases, ranging from age of 5 days to 10 years. The count of reported adverse events by preferred terms included Epistaxis (3517), Heavy menstrual bleeding (3009), Haematoma (1091), Vaginal haemorrhage (1078), Petechiae (989), Intermenstrual bleeding (612), Gingival bleeding (297), Purpura (257), Conjunctival haemorrhage (237), Ecchymosis (236), Haemoptysis (213), Eye haemorrhage (207), Rectal haemorrhage (196), Haematuria (177), Haematochezia (172), Haematemesis (114), Mouth haemorrhage (101), Haemorrhage urinary tract (68), Uterine haemorrhage (56), Anal haemorrhage (49), Gastrointestinal haemorrhage (44), Haemorrhage subcutaneous (41), Genital haemorrhage (36), Urinary bladder haemorrhage (33), Melaena (31), Small intestinal haemorrhage (29), Ear haemorrhage (26), Menometrorrhagia (26), Gastric haemorrhage (14), Pulmonary haemorrhage (14), Intestinal haemorrhage (13), Mucosal haemorrhage (13), Abnormal uterine bleeding (8), Lip haemorrhage (7), Paranasal sinus haemorrhage (6), Penile haemorrhage (6), Tongue haemorrhage (6), Upper gastrointestinal haemorrhage (6), Respiratory tract haemorrhage (5), Mucocutaneous haemorrhage (3), Pharyngeal haemorrhage (3), Pulmonary alveolar haemorrhage (3), Lower gastrointestinal haemorrhage (2), Cervix haemorrhage uterine (1), Oesophageal haemorrhage (1), Tonsillar haemorrhage (1), Urethral haemorrhage (1).

A detailed medical review of the 939 serious, medically confirmed cases was performed which included case reports with 1085 adverse events. Outcome of the 1085 events were as follows: 26 events died/fatal, 327 events resolved, 06 events resolved with sequelae, 232 events resolving, 231 events not resolved and 263 events with unknown outcome.

Of the 1085 events, time to onset from first dose for the 268 events were unknown (either vaccination start date or event onset date was not reported). Time to onset (TTO) from first dose for remaining 817 events was as follows: less than 01 day for 120 events, 01 to 05 days for 279 events, 06 to 15 days for 273 events and more than 15 days for 145 events.

Of the 1085 events, duration of the 942 adverse events was unknown (either event start date or event stop date were not reported), duration for the remaining 143 adverse events was as

follows: less than 01 day for 21 events, 01 to 05 days for 68 events, 06 to 10 days for 27 events and more than 10 days for 27 events.

Of the 939 serious, medically confirmed cases, 23 were reported with fatal adverse events (26 events), out of which 08 cases do not have co-reported event other than event of mucocutaneous bleeding which can contribute to fatal outcome.

Of the 23 medically confirmed fatal case report, in 5 cases time to death from vaccination date with COVID-19 VACCINE ASTRAZENECA is unknown. For remaining 18 medically confirmed fatal case, time to death from vaccination with COVID-19 VACCINE ASTRAZENECA is as follows: 1 - 5 days: 4 cases, 6 - 10 days: 2 cases, 11 - 20 days: 3 cases, more than 20 days: 9 cases.

Of these 23 medically confirmed fatal cases, 8 cases did not contain information regarding medical history or concurrent condition for further assessment. For the remaining 15 cases patients had medical history/concurrent condition of hypertension (5), diabetes mellitus (4), gallbladder polyp (2), splenomegaly (2), anaemia (1), aortic valve stenosis (1), arteriosclerosis coronary artery (1), atrial fibrillation (1), autoimmune thyroiditis (1), benign prostatic hyperplasia (1), cardiac failure (1), cardiovascular event (1), coronary artery disease (1), hypercholesterolaemia (1), hypogammaglobulinemia (1), myocardial infarction (1), myocardial ischaemia (1), neoplasm (1), parkinson's disease (1), plasma cell myeloma (1), renal failure (1), seizure (1), suspected covid-19 (1).

Of the 939 serious, medically confirmed cases, 1 case was found duplicate of another case and in 21 cases the following events were incorrectly coded: Epistaxis (4), Petechiae (4), Haematoma (3), Heavy menstrual bleeding (2), Ecchymosis (1), Eye haemorrhage (1), Haematemesis (1), Haematochezia (1), Haematuria (1), Intermenstrual bleeding (1), Mouth Haemorrhage (1), Rectal haemorrhage (1). Of the remaining cases, 917 serious, medically confirmed cases, 2 contained events (Gastrointestinal haemorrhage and Vaginal Haemorrhage), which occurred prior to vaccination. In 1 case the patient did not receive COVID-19 VACCINE ASTRAZENECA vaccine (patient received Moderna vaccine).

In 75 cases, patient had medical history or concurrent conditions of TCP (23), Thrombosis (10), Platelet count decrease (2), heavy menstrual bleeding/ intermenstrual bleeding (5), haemorrhage (9), Haematemesis (2), Thromboangitis obliterans (2), Thrombophlebitis (1), Activated partial thromboplastin time prolonged (1), Epistaxis (8) Haematoma (2), Petechiae (5), Factor VII deficiency (1), Factor V Leiden mutation (2), Factor II mutation (1), Alcoholic liver disease (2), Chronic myeloid leukaemia (1), Platelet disorder (1), Hepatic enzyme increased. In 8 cases, patients were concomitantly taking Apixaban (2), Pegfilgastrim (1), Montelukast (1), Amlodipine, esomeprazole, and pitavastatin (1), Clopidogrel and Acido acetilsalicilico acetylin (1), Filgrastim (1) and rivaroxaban (1). In 274 cases patient experienced adverse event of TCP (221), Immune TCP (80), Platelet count decreased (26),

Heparin-induced TCP test positive (5), Thrombocytopenic purpura (4), Thrombocytosis (2), Coagulation factor increased (1), Factor XIII deficiency (1), Spontaneous heparin-induced thrombocytopenia syndrome (1) along with mucocutaneous bleeding events..

Of the 939 cases, there were 19 cases where patient received two doses of AZ vaccine and in 14 cases events occurred after the second dose of vaccine.

The medical concept of Mucocutaneous bleeding is not included in the ACCESS programme. Also, since the medical concept of Mucocutaneous bleeding covers a wide range of disorders, it is not feasible to establish the background rate and therefore present the O/E analysis.

Conclusion

The majority of these cases were not medically confirmed. The qualitative medical review of the 939 serious, medically confirmed cases of Mucocutaneous bleeding did not suggest a causal association between COVID-19 VACCINE ASTRAZENECA and Mucocutaneous bleeding.

Based on the currently available information, AstraZeneca did not find evidence of a new or emerging signal for Mucocutaneous bleeding to suggest a need to update the product information or risk management plan. The topic of Mucocutaneous bleeding will continue to be monitored as part of AstraZeneca's routine surveillance efforts.

15.2.3 Tinnitus

Tinnitus is a common medical symptom that can be debilitating. Risk factors include hearing loss, ototoxic medication, head injury, and depression. At presentation, the possibilities of otological disease, anxiety, and depression should be considered. Prevalence studies of tinnitus have mostly been done in western Europe or the US, and have methodological drawbacks, especially with production of an unambiguous definition of tinnitus and phrasing of appropriate epidemiological questions. Consequently, the scatter of prevalence estimates is wide, although most study results have shown rates of between 10% and 15% in the adult population. (Baguley et al 2013). The prevalence of frequent tinnitus is highest among older adults, non-Hispanic whites, former smokers, and adults with hypertension, hearing impairment, loud noise exposure, or generalised anxiety disorder (Shargorodsky et al 2010).

The condition can occur in association with several otological diseases, including otosclerosis, Ménière's disease, and vestibular schwannoma (acoustic neuroma). Tinnitus also has several comorbidities, particularly anxiety, depression and dysfunction of the temporomandibular joint (Baguley et al 2013).

A review of tinnitus, provided in the MSSR (reporting period 01 April 2021 to 30 April 2021) did not indicate any pattern or cluster suggesting a potential safety concern.

Further, a cumulative search of the AstraZeneca global safety database using the MedDRA PT: Tinnitus, was done through 28 June 2021 to identify serious and non-serious cases of Tinnitus, from the COVID-19 VACCINE ASTRAZENECA post-marketing data.

The search of the AstraZeneca global safety database identified a cumulative total of 4328 processed case reports of Tinnitus with COVID-19 ASTRAZENECA VACCINE. Of the 4328 reports of Tinnitus, 63.2% of were reported in females and 32.2% were in males. Gender was not reported in the remaining 4.5% of cases. Age ranged from 18 to < 65 years in 74.1% of the reports, ≥ 65 years in 13.9%, and 0.18% in < 18 years of age. Age was not reported in the remaining 11.9% of cases. The majority of reports (98.5%) were received from spontaneous sources, and the remaining reports (1.5%) were received from regulatory agencies. The majority of reports (91.9%) were not medically confirmed with the remaining 8.1% being medically confirmed. Of these 4328 events of tinnitus, 4342 (54.1%) were considered serious. None of the events had a fatal outcome.

Information on TTO from vaccination with COVID-19 VACCINE ASTRAZENECA to tinnitus was available in 2941 of the 4328 events. Most of the events (37.9%) occurred within 1 day of vaccination, 15.6% occurred 2 to 5 days post-vaccination, 6.4% occurred between 6 to 10 days post-vaccination and another 8.1% occurred > 10 days after vaccination.

Outcome was reported in 3743 of the 4328 events of tinnitus, with 13.1% reported as Recovered, 13.8% as Recovering, 58.5% Not recovered, and 1.0% as Recovered with sequelae.

The vast majority of tinnitus events occurred in combination with concomitant contributing events for Tinnitus such as reactogenic events, including pyrexia/fever/chills (35.3%), fatigue (21.4%), myalgia (11.8%) headache/migraine (40.8%). Moreover, many events were confounded by medical history (ie, pre-existing tinnitus, ear infection, Ménière's disease, labyrinthitis, otitis media, otosclerosis, suspected COVID-19, stroke, hypertension, rheumatoid arthritis, radiotherapy, meningitis, systemic lupus erythematosus, multiple sclerosis); and concomitant medications that may increase the risk of tinnitus (ie, azithromycin, bumetanide, celecoxib, clarithromycin, dapsone, diclofenac, doxazosin, doxepin, doxycycline, erythromycin, etoricoxib, famotidine, flecainide, furosemide, gentamicin, hydroxychloroquine, ibuprofen, isotretinoin, methotrexate, morphine, naproxen, omeprazole, prazosin and sertraline).

An O/E analysis of tinnitus is provided in Table 15. 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 28 June 2021 was 110580529 doses.

Table 15 Observed Versus Expected Analyses for Tinnitus Cases

Medical concept	Observed cases	Expected cases	Risk window (days)	Background rate per 100,000 person-years	Rate ratio (CI 95%)
Tinnitus within 14 days, excluding unknown TTO	3142	10596.57	14	250	0.3 (0.29 - 0.31)
Tinnitus within 14 days, including unknown TTO	4208	10596.57	14	250	0.4 (0.39 – 0.41)
Tinnitus within 28 days, excluding unknown TTO	3311	21193.14	28	250	0.16 (0.15 – 0.16)
Tinnitus within 28 days, including unknown TTO	4377	21193.14	28	250	0.21 (0.2 – 0.21)

CI Confidence Interval, TTO Time To Onset.

Conclusion

This cumulative review of tinnitus 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. Tinnitus will continue to be monitored as part of AstraZeneca's routine surveillance process.

15.2.4 Serious hypertension

A cumulative search of the AstraZeneca Global Patient Safety Database was conducted on 29 June 2021 for adverse event reports of Serious Hypertension in association with the use of COVID-19 VACCINE ASTRAZENECA. The search terms included (MedDRA PTs): Hypertension; BP and Malignant Hypertension.

The search identified 7750 cases (7700 spontaneous, 50 non-interventional/post-marketed) (1915 serious and 5835 non-serious events) with 7810 adverse events related to Serious Hypertension as follows: Blood Pressure Increased (5032), Hypertension (2771) and Malignant Hypertension (7). Of the 7750 cases, 4773 cases were medically confirmed and 2977 were not medically confirmed. Of the 4773 cases, 504 were serious.

There were 4628 females (59.7.%), 3014 males (38.9%), and 108 (1.4%) of unknown gender. In 2 cases (0.0%) of 7750 cases, the age range was 0 to <18 years, in 5518 cases (71.2%) the age group was 18 to <65 years, in 1835 cases (23.7%) the age group was 65+ years, in 28

cases (0.4%) the age group was adult, in 12 cases (0.2%) the age group was elderly and for the remaining 355 cases (4.6%) the age was missing and not provided.

Table 16 Serious Hypertension Events Cumulatively until 29 June 2021

Preferred Term	# Events
Blood pressure increased	5026
Hypertension	2756
Malignant hypertension	7

Time to onset for the events (Table 17) is shown below:

Table 17 TTO Serious Hypertension Events Cumulatively until 29 June 2021

Time First Dose To Case Onset	# of Events	%
00 Under 1 day	4690	59.8
01 day	650	8.3
02 days	214	2.7
03 days	127	1.6
04 days	116	1.5
05 days	70	0.9
06 days	61	0.8
07 days	55	0.7
08 days	48	0.6
09 days	35	0.4
10 to 15 days	122	1.6
16 to 20 days	76	1.0
21 to 30 days	74	0.9
31 to 40 days	25	0.3
41 to 60 days	30	0.4
61 to 80 days	27	0.3
81 to 100 days	11	0.1
Over 100 to 200 days	2	0.0
Over 1 year	6	0.1
Undefined (missing)	1404	17.9

TTO Time To Onset.

For the 7750 cases, the case outcomes were as follows: 4268 events recovered, 59 were recovered with sequelae, 1294 were recovering, 1432 were not recovered, 27 were missing, 29 with fatal outcome and 641 events where the outcome was unknown (Table 18).

Table 18 Outcome for Serious Hypertension Cases Cumulatively until 29 June 2021

Case Outcome	# of Cases	%
Died	29	0.4
Not Recovered	1432	18.5
Recovered	4268	55.1
Recovering	1294	16.7
Recovered With Sequelae	59	0.8
Missing	27	0.3
Unknown	641	8.3

In 4610 cases the AE had resolved or recovered with sequelae duration was available in 13% of cases (614 out of 4610).

Median duration was 1 day (range 0 to 63 days). In 75% (458) of the cases the duration was ≤ 3 days.

In 504 cases of the serious and medically confirmed case reports, 29 cases were fatal. Causes of death included adverse event following immunisation, hyperlipidaemia, type 2 diabetes mellitus, COPD, TCP, pneumonia, CVST, vomiting and cerebral haemorrhage. In 3 cases the cause of death was only hypertension.

From the 7750 cases for 'Serious Hypertension' the serious and medically confirmed cases were: 504 cases and were analysed individually. From these 504 cases the following information was noted.

Relevant Medical History in Cases Reporting Serious Hypertension:

504 out of the 7750 cases had relevant medical history or risks factors. Of those 504 cases, relevant medical history was grouped into the following categories and most frequent confounders are: hypertension (141 cases), elderly age (126 cases), obesity (67 cases), diabetes mellitus (30 cases), allergy (21 cases), hypothyroidism (21 cases), asthma (16 cases), hypercholesterolaemia (11 cases), arthritis (9 cases), COVID-19 (7 cases), myocardial ischaemia (7 cases), tobacco user (7 cases), depression (7 cases), migraine (7 cases) and chronic renal failure (6 cases) (Table 19).

Table 19 Serious Hypertension Confounding Medical History Cumulatively until 29 June 2021

Confounders to Medical History	No. of Cases
Hypertension: (hypertension arterial, high blood pressure, essential hypertension, increased blood pressure, blood pressure high, gestational hypertension, jumps in blood pressure, blood pressure disorder)	141
Elderly age: (above 66 years)	126
Obesity: (obesity: 41 cases, overweight- 26 cases)	67
Diabetes mellitus: (type 2 diabetes mellitus, pre-diabetes, type 1 diabetes mellitus, diabetic ketoacidosis, insulin resistance, diabetes insipidus)	30
Allergy: (multiple allergies, drug allergy, rhinitis allergy, pollen allergy, house dust allergy)	21
Hypothyroidism: (hashimoto hypothyroidism, underactive thyroid, Thyroid function decrease, hypothyreosis, hashimoto thyroiditis, autoimmune thyroiditis, thyroidectomy)	21
Asthma	16
Hypercholesterolaemia: (cholesterol high, blood cholesterol, hypercholesterolaemia, high LDL cholesterol), hyperlipidaemia	11
Arthritis: (rheumatoid arthritis, osteoarthritis knee, degenerative joint disease, gout)	9
Covid-19: (suspected COVID-19, COVID-19 respiratory infection),	7
Anaemia: (anaemia macrocytic, anemia, chronic anemia)	4
Myocardial ischaemia	7
Tobacco user: (Smoking, current smoker, tobacco user, ex-smoker)	7
Depression: (chronic depression, anxiety depression, anxiodepressive syndrome)	7
Migraine	7
Headache	2
Chronic renal failure: (renal insufficiency, renal failure, chronic kidney disease)	6
Tachycardia: (high pulse rate, tachycardia, palpitations)	5
Pulmonary embolism	5

Table 19 Serious Hypertension Confounding Medical History Cumulatively until 29 June 2021

Confounders to Medical History	No. of Cases
Epilepsy: (epilepsy, epileptic fit, seizures)	5
Myocardial infarction: (infarction, heart attack)	4
Atrial fibrillation	4
Cerebrovascular accident	3
Gastritis	3
Chronic obstructive pulmonary disease	3
Dyslipidaemia	3
Ischaemic stroke	2
Angina pectoris	2
Alzheimer's disease	2
Hyperthyroidism	2
Esophagitis	2
Raynauds syndrome	2
Peripheral arterial occlusive disease	2
Peripheral venous disease (venous insufficiency)	2
Fibromyalgia	2
Deep vein thrombosis	2
Hypotension	2

COVID-19 Coronavirus Disease 2019, LDL Low Density Lipoprotein.

Twenty-two percent (112/22%) originated from France and the other cases (>10) were from the following countries: United Kingdom (81), Philippines (64), Italy (45), Germany (18), Norway (17), Sweden (16), Spain (16), Portugal (16), Finland (13), Denmark (12), Croatia (11) and Belgium (11).

In 504 cases of the serious and medically confirmed case reports, BP values were available in 98 (19.44%) of reports. In 55 reports, the reported BP readings were ≥180/≥110 mmHg.

In 55 cases where BP≥ 180/≥110 mmHg; 19 were resolved, 13 were not resolved, 13 resolving, 10 reports the outcome was not provided/unknown.

Review of Serious Hypertension and Related Terms Cases:

We performed a thorough review of all the serious and medically confirmed cases and no signal was detected.

Most of the cases reported that were related to serious hypertension included the risk factors hypertension, elderly age, obesity and diabetes mellitus. Adults over the age of 50 years old account for approximately 60% of the 7750 cases.

Observed versus Expected Analysis for Serious Hypertension:

From the 7750 cases the O/E ratio was 0.11 (95% CI: 0.1-0.11) the observed number of cases was significantly lower than the expected number of cases 72924. Similarly, from the 504 serious and medically confirmed cases the O/E ratio was 0.01 (95% CI : 0.01-0.01) the observed number of cases was significantly lower than the expected number of cases 72924.

No trend was observed to suggest a higher incidence than expected after receiving COVID-19 VACCINE ASTRAZENECA.

Literature Review Search Strategy:

A search of Embase database was undertaken on 07 July 2021 using the following combination of search terms: Hypertension; BP Increased and Malignant Hypertension.

The search yielded 189 results and revealed no relevant article for Serious Hypertension.

Summary and Conclusion

From the 7750 cases for 'Serious Hypertension' the serious and medically confirmed cases were derived (504 cases) and analysed individually. Of the 504 cases no signal was detected. These 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. In addition to the analysis of the 504 cases, no relevant literature article was noted to be of safety concern. The O/E analysis for all reported cases of serious hypertension showed that observed cases occurred significantly less frequently than expected.

Given the overall post-marketing exposure to COVID-19 VACCINE ASTRAZENECA, the number of potential serious hypertension cases reported in the COVID-19 VACCINE ASTRAZENECA vaccinated population is considered low, especially taking into account that most cases retrieved with the above PTs, did not correspond to a serious hypertension per se, due to limited information or to other diseases.

Based on available data as of 29 June 2021, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between COVID-19 VACCINE ASTRAZENECA and serious hypertension. No update to the core product information or RMP is warranted at this time. AstraZeneca will continue to monitor safety information for serious hypertension from all available sources as part of the routine safety surveillance.

15.2.5 Vertigo

Vertigo is a common presenting complaint in primary care offices and emergency departments. It is a symptom of vestibular dysfunction and has been described as a sensation of motion, most commonly rotational motion. It is important to differentiate vertiginous symptoms from other forms of dizziness, such as light-headedness, which is most often associated with presyncope (Labuguen 2006). Vertigo affects all ages. In younger patients, middle ear pathology is most often the cause. In the elderly, specific assessment is needed due to the risk of falls and their complications (Bouccara et al 2018).

Vertigo affects both men and women but is about 2 to 3 times more common in women than men (Stanton and Freeman 2021). It has been associated with various comorbid conditions, including depression and cardiovascular disease. Prevalence increases with age and varies depending on the underlying diagnosis. Based on a survey of the general population, the 1 year prevalence of vertigo is about 5% and an annual incidence of 1.4%. Dizziness including vertigo affects about 15% to over 20% of adults yearly (Neuhauser 2016). For benign paroxysmal positional vertigo, the 1-year prevalence is about 1.6%, and it is less than 1% for vestibular migraine.

A review of Vertigo, provided in the MSSR (reporting period 01 April 2021 to 30 April 2021) did not indicate any pattern or cluster suggesting a potential safety concern.

Further, a cumulative search of the AstraZeneca global safety database using the MedDRA PT Vertigo was done through 28 June 2021 to identify serious cases of Vertigo from the COVID-19 VACCINE ASTRAZENECA post-marketing data. The search of the AstraZeneca global safety database identified a cumulative total of 3863 closed reports of Vertigo with COVID-19 VACCINE ASTRAZENECA.

Of the 3863 closed reports of Vertigo, 73.2% were reported in females and 23.8% were in males. Gender was not reported in the remaining 3.0% of cases. Age ranged from 18 years to < 65 years in 74.0% of the reports, ≥ 65 years in 17.3%, and 0.2% in < 18 years of age. Age was not reported in the remaining 8.4% of cases. The majority of reports (98.6%) were received from spontaneous sources, and the remaining reports (1.4%) were received from regulatory agencies. The majority of reports (78.1%) were not medically confirmed with the remaining 21.9% being medically confirmed.

Of these 3863 events of Vertigo, 1903 (49.3%) were considered serious. None of the events had a fatal outcome.

The vast majority of events occurred in combination with concomitant contributing events such as pyrexia/fever/chills, fatigue and headache/migraine. Moreover, many events were confounded by medical history (ie, suspected COVID-19, cerebrovascular accident,

preexisting vertigo, tinnitus, ear infection, Ménière's disease, labyrinthitis, otitis media, radiotherapy, meningitis and multiple sclerosis); and concomitant medications that may increase the risk of vertigo (ie, celecoxib, codeine, hydroxychloroquine, indapamide, lansoprazole, naproxen, omeprazole and pregabalin).

An observed and expected analysis of vertigo is provided below (Table 20). 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 28 June 2021 was 110580529 doses.

Table 20 Observed Versus Expected Analyses for Vertigo Cases

Medical concept	**Observed cases**	**Expected cases**	**Risk window (days)**	**Background rate per 100,000 person-years**	**Rate ratio (CI 95%)**
Vertigo within 14 days, excluding unknown TTO	2975	63185.24	14	1490.7	0.05 (0.05 – 0.05)
Vertigo within 14 days, including unknown TTO	3895	63185.24	14	1490.7	0.06 (0.06 – 0.06)
Vertigo within 28 days, excluding unknown TTO	3113	126370.48	28	1490.7	0.02 (0.02 – 0.03)
Vertigo within 28 days, including unknown TTO	4032	126370.48	28	1490.7	0.03 (0.3 – 0.03)

CI Confidence Interval, TTO Time To Onset.

Conclusion

This cumulative review of vertigo 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. Vertigo will continue to be monitored as part of AstraZeneca's routine surveillance process.

15.2.6 Viral herpes infection

As requested by PRAC, a cumulative review of Herpes viral infections is presented with a cut-off date of 28 June 2021. The AstraZeneca global safety database was searched using the following MedDRA (v24.0) PTs:

Colitis herpes, Disseminated varicella, Disseminated varicella zoster virus infection, Eczema herpeticum, Examthema subitem, Gastritis herpes, Genital herpes, Genital herpes simplex, Genital herpes zoster, Haemorrhagic varicella syndrome, Herpes dermatitis, Herpes oesophagitis, Herpes ophthalmic, Herpes pharyngitis, Herpes sepsis, Herpes simplex, Herpes simplex bronchitis, Herpes simplex cervicitis, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex reactivation, Herpes simplex sepsis, Herpes simplex viraemia, Herpes simplex visceral, Herpes virus infection, Herpes zoster, Herpes zoster cutaneous disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster meningoradiculitis, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Herpes zoster pharyngitis, Herpes zoster reactivation, Herpetic radiculopathy, Human herpes virus 6 encephalitis, Human herpes virus 6 infection, Human herpes virus 6 infection reactivation, Human herpes virus 7 infection, Human herpes virus 8 infection, Kaposi sarcoma inflammatory cytokine syndrome, Lower respiratory tract herpes infection, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Nasal herpes, Necrotising herpetic retinopathy, Ophthlamic herpes simplex, Ophthlamic herpes zoster, Oral herpes, Pneumonia herpes viral, Proctitis herpes, Varicella, Varicella keratitis, Varicella post vaccine, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia, Varicella zoster sepsis, Varicella zoster virus infection.

The search identified a total of 3200 cases. Out of the 3200 cases (3265 events), 2630 cases (82.18%) were not medically confirmed, 1656 (51.75%) cases were reported as serious, out of which 179 cases were medically confirmed and 1 case where adverse event of Herpes simplex hepatitis was reported with a fatal outcome.

Out of the 3200 cases, age was reported in 2854 cases, ranging from 16 – 97 years and a median of 57 years. Incorrect age was provided in 3 cases ranging from age of 3 weeks to 2 months. The count of reported adverse events by preferred terms included Herpes zoster (1996), Oral herpes (955), Herpes simplex (84), Genital herpes (73), Varicella (35), Nasal herpes (30), Herpes ophthalmic (29), Herpes zoster oticus (18), Herpes simplex reactivation (14), Herpes zoster reactivation (5), Varicella zoster virus infection (5), Eczema herpeticum (4), Herpes dermatitis (4), Herpes zoster cutaneous disseminated (3), Disseminated varicella zoster virus infection (2), Genital herpes simplex (2), Colitis herpes (1), Haemorrhagic varicella syndrome (1), Herpes simplex encephalitis (1), Herpes simplex hepatitis (1), Herpes zoster meningitis (1), Meningoencephalitis herpetic (1).

A detailed medical review of the 179 serious, medically confirmed cases was performed. Of the 179 cases, there were 9 cases where patient received two doses of vaccine (8 patients

received COVID-19 VACCINE ASTRAZENECA and in 1 patient, 2nd dose of which vaccine taken was not specified), 3 cases where event of Herpes zoster was incorrectly coded, 1 case where event of Herpes zoster had occurred prior to vaccination with COVID-19 ASTRAZENECA VACCINE, 26 cases where patients had concurrent infection (including Herpes or COVID 19), 10 cases where patients were immunocompromised, 3 cases where patients were concomitantly using systemic steroids and 8 cases were confounded by diabetes mellitus. Remaining 128 cases had limited information for further case assessment.

179 serious medically confirmed case reports included 183 events. Outcome of the 183 events was as follows: 1 event died/fatal, 41 events resolved, 8 events resolved with sequelae, 53 events resolving, 53 events not resolved and 27 events with unknown outcome.

Of the 183 events, time to onset from first dose for the 36 events were unknown (either vaccination start date or event onset date was not report). Time to onset from first dose for remaining 147 events was as follows: less than 1 day: 22 events, 1 - 5 days: 44 events, 6 - 15 days: 44 events, and more than 15 days: 37 events.

Of the 183 events, duration of the 163 adverse events was unknown (either event start date or event stop date is unknown), duration for the remaining 143 adverse events was as follows: 1 - 5 days: 5 events, 6 - 10 days: 5 events, and more than 10 days: 10 events.

One case report (PPD) with fatal outcome refers to PPD-year-old PPD patient with history of PPD No concomitant products were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD . On PPD , the patient experienced herpes simplex hepatitis. On PPD , the patient experienced PPD and disseminated intravascular coagulation. The patient 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 medical concept of Herpes viral infections is not included in the ACCESS programme. Also, since the medical concept of Herpes viral infections covers a wide range of disorders, it is not feasible to establish the background rate and therefore present the O/E analysis.

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 at this time. Viral herpes infection will continue to be monitored as part of AstraZeneca's routine surveillance process..

15.2.7 Pulmonary Embolism

In the PRAC Assessment Report for the May 2021 Monthly Summary Safety Report (Review period: 01 May 2021 – 31 May 2021), AstraZeneca received a request to provide an Observed vs. Expected analysis for Pulmonary embolism. The results of this analysis using a 28 day RW and including age and gender stratifications are provided in Table 21. Results of this analysis show that the observed number of cases of pulmonary embolism with COVID-19 VACCINE ASTRAZENECA are less than the expected number overall and for each age and gender stratification.

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
O/E Analysis – Excluding cases with unknown Time to Onset (TTO)							
Pulmonary embolism – Excluding cases with unknown TTO	28	169.42	110580529	1766	14362.17	0.12 (0.12 - 0.13)	Observed significantly < expected
Pulmonary embolism: 18-49 years excluding cases with unknown TTO (EEA/UK)	28	85.62	23883226	297	1567.63	0.19 (0.17 - 0.21)	Observed significantly < expected
Pulmonary embolism: 50-59 years excluding cases with unknown TTO (EEA/UK)	28	195.76	18157095	275	2724.88	0.1 (0.09 - 0.11)	Observed significantly < expected
Pulmonary embolism: 60-69 years excluding cases with unknown TTO (EEA/UK)	28	300.39	22337254	464	5143.89	0.09 (0.08 - 0.1)	Observed significantly < expected
Pulmonary embolism: 70-79 years excluding cases with unknown TTO (EEA/UK)	28	632.07	12164855	369	5894.53	0.06 (0.06 - 0.07)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
Pulmonary embolism: ≥80 years excluding cases with unknown TTO (EEA/UK)	28	877.98	3509828	114	2362.37	0.05 (0.04 - 0.06)	Observed significantly < expected
Pulmonary embolism: Females, 18 – 49 years excluding cases with unknown TTO (UK)	28	104.25	7535741	84	602.25	0.14 (0.11 - 0.17)	Observed significantly < expected
Pulmonary embolism: Females, 50 – 59 years excluding cases with unknown TTO (UK)	28	174.98	6160471	66	826.38	0.08 (0.06 - 0.1)	Observed significantly < expected
Pulmonary embolism: Females, 60 – 69 years excluding cases with unknown TTO (UK)	28	262.76	4710221	70	948.81	0.07 (0.06 - 0.09)	Observed significantly < expected
Pulmonary embolism: Females, 70 – 79 years	28	604.53	3457691	71	1602.44	0.04 (0.03 - 0.06)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
excluding cases with unknown TTO (UK)							
Pulmonary embolism: Females, ≥80 years excluding cases with unknown TTO (UK)	28	871.37	1600649	35	1069.24	0.03 (0.02 - 0.05)	Observed significantly < expected
Pulmonary embolism: Males, 18 – 49 years excluding cases with unknown TTO (UK)	28	65.63	6635899	75	333.87	0.22 (0.18 - 0.28)	Observed significantly < expected
Pulmonary embolism: Males, 50 – 59 years excluding cases with unknown TTO (UK)	28	218.96	6758081	76	1134.4	0.07 (0.05 - 0.08)	Observed significantly < expected
Pulmonary embolism: Males, 60 – 69 years excluding cases with unknown TTO (UK)	28	342.2	4784978	69	1255.27	0.05 (0.04 - 0.07)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
Pulmonary embolism: Males, 70 – 79 years excluding cases with unknown TTO (UK)	28	664.52	3116346	66	1587.56	0.04 (0.03 - 0.05)	Observed significantly < expected
Pulmonary embolism: Males, ≥80 years excluding cases with unknown TTO (UK)	28	887.39	950471	16	646.59	0.02 (0.01 - 0.04)	Observed significantly < expected
O/E Analysis – Including cases with unknown Time to Onset (TTO)							
Pulmonary embolism – Including cases with unknown TTO	28	169.42	110580529	2544	14362.17	0.18 (0.17 - 0.18)	Observed significantly < expected
Pulmonary embolism: 18-49 years including cases with unknown TTO (EEA/UK)	28	85.62	23883226	445	1567.63	0.28 (0.26 - 0.31)	Observed significantly < expected
Pulmonary embolism: 50-59 years including	28	195.76	18157095	388	2724.88	0.14 (0.13 - 0.16)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
cases with unknown TTO (EEA/UK)							
Pulmonary embolism: 60-69 years including cases with unknown TTO (EEA/UK)	28	300.39	22337254	565	5143.89	0.11 (0.1 - 0.12)	Observed significantly < expected
Pulmonary embolism: 70-79 years including cases with unknown TTO(EEA/UK)	28	632.07	12164855	451	5894.53	0.08 (0.07 - 0.08)	Observed significantly < expected
Pulmonary embolism: ≥80 years including cases with unknown TTO (EEA/UK)	28	877.98	3509828	159	2362.37	0.07 (0.06 - 0.08)	Observed significantly < expected
Pulmonary embolism: Females, 50-59 years including cases with unknown TTO (UK)	28	104.25	7535741	172	602.25	0.29 (0.24 - 0.33)	Observed significantly < expected
Pulmonary embolism: Females, 60-69 years	28	174.98	6160471	102	826.38	0.12 (0.1 - 0.15)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
including cases with unknown TTO (UK)							
Pulmonary embolism: Females, 70-79 years including cases with unknown TTO (UK)	28	262.76	4710221	108	948.81	0.11 (0.09 - 0.14)	Observed significantly < expected
Pulmonary embolism: Females, ≥80 years excluding cases with unknown TTO (UK)	28	604.53	3457691	99	1602.44	0.06 (0.05 - 0.08)	Observed significantly < expected
Pulmonary embolism: Males, 18 – 49 years including cases with unknown TTO (UK)	28	871.37	1600649	57	1069.24	0.05 (0.04 - 0.07)	Observed significantly < expected
Pulmonary embolism: Males, 50 – 59 years including cases with unknown TTO (UK)	28	65.63	6635899	113	333.87	0.34 (0.28 - 0.41)	Observed significantly < expected

Table 21 Observed versus expected analyses for Pulmonary embolism cases stratified by gender, age group and with known and unknown time-to-onsets in EU and UK as of 28 June 2021

Pulmonary Embolism by age groups (years) and gender	Risk Window (days)	Incidence rates (per 100,000)	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
Pulmonary embolism: Males, 60 – 69 years including cases with unknown TTO (UK)	28	218.96	6758081	130	1134.4	0.11 (0.1 - 0.14)	Observed significantly < expected
Pulmonary embolism: Males, 70 – 79 years including cases with unknown TTO (UK)	28	342.2	4784978	107	1255.27	0.09 (0.07 - 0.1)	Observed significantly < expected
Pulmonary embolism: Males, ≥80 years including cases with unknown TTO (UK)	28	664.52	3116346	99	1587.56	0.06 (0.05 - 0.08)	Observed significantly < expected

CI Confidence Interval, DLP Data Lock Point, EEA European Economic Area, EU European Union, O/E observed or expected, TTO Time To Onset, UK United Kingdom.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of safety concerns

At the beginning of the reporting period, there was no safety specification, presented in a global AstraZeneca Core RMP, in effect for COVID-19 VACCINE ASTRAZENECA. However, a Core RMP was developed during the reporting period (Version no. 1.0, dated 15 February 2021 which included the following important identified risks, important potential risks, and missing information (see Table 22).

Table 22 Summary of safety concerns – Core RMP for COVID-19 VACCINE ASTRAZENECA (Version 1.0; dated 15 February 2021)

Risk category	Safety concern
Important identified risks	None
Important potential risks	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

COVID-19 Coronavirus Disease 2019, RMP Risk Management Plan, VAED: Vaccine-associated enhanced disease.

During the reporting period, the Core RMP was updated to include safety concerns from the post-marketing experience. At the end of the reporting period, the safety specification as per CoreRMP are mentioned in Table 23.

Table 23 Summary of Safety Concerns: AstraZeneca Core RMP (Version 3.0; dated 28 April 2021)

Section/Topic	Core RMP
Important Identified Risk	Thrombosis in combination with thrombocytopenia
Important Potential Risk	Immune-mediated neurological conditions. Vaccine-associated enhanced disease (VAED).

Table 23 Summary of Safety Concerns: AstraZeneca Core RMP (Version 3.0; dated 28 April 2021)

Section/Topic	Core RMP
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.

COVID-19 Coronavirus Disease 2019, RMP Risk Management Plan, VAED Vaccine-Associated Enhanced Disease.

Data relevant to the Core RMP during the reporting period are discussed in subsequent sub-sections below.

16.2 Signal evaluation

Three validated signals were closed during the reporting period: Hypersensitivity including anaphylaxis, Thrombotic events with thrombocytopenia, and TCP. A summary of these signal evaluations 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 were no closed signals categorised as important potential risks during the reporting period.

16.2.3 Closed signals categorised as important identified risks

There was 1 closed signal, Thrombotic events with TCP, that was categorized as important identified risk during the reporting period.

16.2.3.1 Thrombotic events with thrombocytopenia

Table 24 Thrombotic events with thrombocytopenia

Characterisation	Summary
Source of the signal	Qualitative data analysis (Individual Case Safety Report or Case Series); Regulatory Authority

Table 24 Thrombotic events with thrombocytopenia

Characterisation	Summary
Date detected	11 March 2021
Date closed	13 April 2021
Reference document(s)	March 2021 COVID-19 VACCINE ASTRAZENECA Monthly Safety Summary Report (Review period: 01 March 2021-31 March 2021) April 2021 COVID-19 VACCINE ASTRAZENECA Monthly Safety Summary Report (Review period: 01 April 2021-30 April 2021)
Regulatory Procedure Reference Document	EMEA/H/C/005675/IAIN/0004 (EU imposition from extraordinary PRAC meeting 18 March 2021- EPITT number: 19683)) and EMEA/H/C/005675/IAIN/0010 (An updated preliminary signal assessment report on additional data, round 2, was received from PRAC on 04 April 2021, and an Oral Explanation was held on 06 April 2021. The PRAC final recommendation was to further update sections 4.4 & 4.8 of the SmPC with wording related to embolic and thrombotic events. In addition, corresponding updates have been made to Sections 2 & 4 of the Package Leaflet.
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature of Thrombotic events with thrombocytopenia (HLT: Thrombocytopenias and hematopoietic thrombocytopenia SMQ_Narrow co-reported with events from the Embolic and thrombotic events SMQ) with COVID-19 VACCINE ASTRAZENECA with medical review according to Brighton collaboration.
Outcome of the evaluation	As of 31 March 2021, a total of 184 case reports of thrombotic events with thrombocytopenia involving COVID-19 VACCINE ASTRAZENECA were reviewed. All of these reports were serious and medically confirmed. The majority of cases occurred in females (119) and in the 18-49 year-old age group. A total of 49 cases reported a fatal outcome. For the majority of cases (127), the thromboembolic event occurred within 14 days after vaccination.

Table 24 Thrombotic events with thrombocytopenia

Characterisation	Summary
Conclusions	As a result of AstraZeneca's evaluation and confirmation of the signal of Thrombosis in combination with thrombocytopenia, the COVID-19 VACCINE ASTRAZENECA CDS was updated: Section 4.3 (Contraindications), 4.4 (Special warnings and special precautions for use), and Section 4.8 (Undesirable effects). These updates were internally approved on 19 April 2021. "Thrombosis in combination with thrombocytopenia" was added as an Important Identified Risk to the Core Risk Management Plan on 28 April 2021. "Thrombosis with thrombocytopenia syndrome" is considered an Important Identified Risk in the EU RMP. Thrombotic events with thrombocytopenia is kept under close surveillance by AstraZeneca.

CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, EMEA European Medicines Agency, EU European Union, HLT High Level Term, PRAC Pharmacovigilance Risk Assessment Committee, RMP Risk Management Plan, SmPC Summary of Product Characteristics , SMQ Standardised MedDRA Query.

16.2.4 Closed signals that are potential risks not categorised as important

There were no closed signals that are potential risks not categorised as important during the reporting period.

16.2.5 Closed signals that are identified risks not categorised as important

There were 2 closed signals (Hypersensitivity including anaphylaxis and TCP) that are identified risks not categorised as important during the reporting period.

16.2.5.1 Hypersensitivity including anaphylaxis

Table 25 Hypersensitivity including anaphylaxis

Characterisation	Summary
Source of the signal	Quantitative signal detection system
Date detected	01 February 2021
Date closed	01 March 2021

Table 25 Hypersensitivity including anaphylaxis

Characterisation	Summary
Reference document(s)	February 2021 COVID-19 VACCINE ASTRAZENECA Monthly Safety Summary Report (Review period: 01 February 2021-28 February 2021)
Regulatory Procedure Reference Document	EMEA/H/C/005675/IAIN/0011 (To update section 4.4 & 4.8 of the SmPC and section 4 of the PL to implement the signal recommendations on hypersensitivity and anaphylaxis (EPITT no 19668) as recommended in PRAC Signal Assessment Report dated 11 March 2021.
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature of Hypersensitivity including anaphylaxis (Anaphylactic reaction SMQ_Narrow, Angioedema SMQ_Narrow and PT: Hypersensitivity) with COVID-19 VACCINE ASTRAZENECA with medical review according to Sampson criteria.
Outcome of the evaluation	As of 05 February 2014, 14 cases of Anaphylaxis (7 cases met Sampson criteria of Anaphylaxis) has been reported with COVID-19 VACCINE ASTRAZENECA from post-marketing sources. In 33 cases, either Angioedema or localized oedema/swelling was reported. Anaphylaxis and Angioedema are reported in medica/scientific literature in association with other COVID-19 vaccines with a possible causal association.
Conclusions	Based upon an assessment of available data, AstraZeneca has concluded that there is reasonable possibility of a causal association between COVID-19 VACCINE ASTRAZENECA and serious hypersensitivity including anaphylaxis/anaphylactic reaction. Therefore, the CDS Section 4.4 (Special warnings and special precautions for use) and Section 4.8 (Undesirable effects) has been amended on 01 March 2021 to include information on anaphylaxis/anaphylactic reaction and angioedema as an adverse drug reaction (ADR) associated with COVID-19 VACCINE ASTRAZENECA. Anaphylaxis is considered and Important Identified Risk in the EU RMP.

Table 25 Hypersensitivity including anaphylaxis

Characterisation	Summary
	Anaphylaxis is kept under close surveillance by AstraZeneca.

ADR Adverse Drug Reaction, CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, EU European Union, HLT High Level Term, PL Package Leaflet, PRAC Pharmacovigilance Risk Assessment Committee, RMP Risk Management Plan, SMQ Standardised MedDRA Query.

16.2.5.2 Thrombocytopenia

Table 26 Thrombocytopenia

Characterisation	Summary
Source of the signal	Qualitative data analysis (Individual Case Safety Report or Case Series); Quantitative signal detection system; Regulatory Authority
Date detected	11 March 2021
Date closed	17 June 2021
Reference document(s)	March 2021 COVID-19 VACCINE ASTRAZENECA Monthly Safety Summary Report (Review period: 01 March 2021-31 March 2021) May 2021 COVID-19 VACCINE ASTRAZENECA Monthly Safety Summary Report (Review period: 01 May 2021-31 May 2021)
Regulatory Procedure Reference Document	EMEA/H/C/005675/SDA/034
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature of TCP (Thrombocytopenia HLT and Hematopoietic thrombocytopenia SMQ_Narrow) with COVID-19 VACCINE ASTRAZENECA.
Outcome of the evaluation	A total of 1328 cases of TCP with the above search strategy were retrieved as of 30 April 2021: 671 cases were reported in combination with TCP and 657 cases of TCP without a diagnosis of thrombosis. Of the 1328 reports, 1275 were reported as serious and 894 were medically confirmed. Fatal outcome was reported in 179 of the reports. Approximately 55% (732) of the TCP occurred within 14 days after vaccination, 67% occurred within 21 days, and 76%

Table 26 Thrombocytopenia

Characterisation	Summary
	occurred within 42 days of vaccination. Observed versus expected analysis demonstrated a consistent pattern of observed cases occurring more frequently than expected regardless of risk window or vaccinee demographics, however the majority of events occurred in the 18 - 59 year old age group, regardless of gender.
Conclusions	From the data identified during the reporting period and also taking into account cumulative experience, the COVID-19 VACCINE ASTRAZENECA CDS Section 4.8 was updated on 17 June 2021 to include "thrombocytopenia" as an Adverse Drug Reaction (ADR) with an assigned frequency of 'very rare' (3/33869 = <0.01). As a result of an imposition, "Thrombocytopenia with associated bleeding" was added as an Important Potential Risk to the EU RMP, submitted on 12 August 2021.

ADR Adverse Drug Reaction, CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, EU European Union, PT Preferred Term, RMP Risk Management Plan, SMQ Standardized MedDRA Query.

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 reported is used as 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.

16.3.1 New information on Important Potential Risks

All Important Potential Risks included in Section 16.1 and included in Table 27 below are kept under close surveillance by AstraZeneca.

Table 27 Risks presented in Core RMP (Version 3; dated 28 April 2021)

Section/Topic	Core RMP
Important Potential Risk	• Immune-mediated neurological conditions. • Vaccine-associated enhanced disease (VAED).

RMP Risk Management Plan, VAED Vaccine-Associated Enhanced Disease.

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 PBRER, a total of 3525 cases have reported 3799 PTs within the concept of Immune-mediated neurological disorders. The most commonly reported PTs are Neuralgia (1524), Guillain-Barre syndrome (608), Sensory disturbance (336), Sensory loss (291), Neuropathy peripheral (263), Myelitis transverse (86), Multiple sclerosis (84), Optic neuritis (73), Multiple sclerosis relapse (60), Encephalitis (72), Demyelination (41), Polyneuropathy (40), Myelitis (35), Neuritis (27), Miller-Fisher syndrome (26), Acute disseminated encephalomyelitis(ADEM) (25) and Encephalopathy (21).

16.3.1.1.1 Guillain-Barré Syndrome

After review of cases with data cut-off 31 May 2021, AstraZeneca validated a signal of GBS on 09 June 2021. Pharmacovigilance Risk Assessment Committee also raised additional requests, to which AZ responded to in the July MSSR. In order to provide the most current information, AZ hereby provides the assessment as done for July MSSR with DLP 31 July (and not 28 June), for this topic only.

AstraZeneca convened a panel of independent expert Neurologists [PPD] to review data on GBS cases with a data cut off of 31 July 2021 to assess any possible link of GBS to the COVID vaccination with AstraZeneca vaccine. A copy of the Panel's conclusions is provided in Appendix 11, of which the key findings are also summarised below in this section. The neurology expert panel proposed that the cautionary wording in the EU SmPC on GBS remains, but that causation is not confirmed by the data available to date for the AstraZeneca COVID-19 vaccination.

Review of Cases

Following a request from PRAC in assessment report for the 5th monthly summary safety update , a cumulative review (cut-off date of 31 July 2021), with assessment of cases according to Brighton Collaboration criteria(BCC) is presented below. The Brighton Collaboration is an international collaboration sponsored by the World Health Organization to

facilitate the development, evaluation, and dissemination of high quality internationally standardized case definitions for various illnesses, with the aim of improving vaccine safety. These criteria also account for the level of diagnostic certainty based on the presenting findings at clinical and additional examinations, ranging from level 1 (highest level of diagnostic certainty) to level 4 (reported as Guillain-Barré syndrome, possibly due to insufficient data for further classification) (Fokke et al 2014). A decision tree algorithm for GBS and Miller Fisher Syndromes Level of Diagnostic Certain is presented in Appendix 10 which provides guidance on using available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for GBS or Miller Fisher Syndrome.

As requested by PRAC in Assessment Report for 4th and 5th Monthly Safety Update all confirmed cases of Guillain-Barre syndrome (ie, cases that fulfil BCC level 1-3) have been classified according to WHO Uppsala Monitoring Centre (UMC) criteria for causal drug association. Cumulative analysis using WHO-UMC criteria for all cases of GBS fulfilling BCC Level 1-3 are provided below.

Overview of cases

Cumulatively until 31 July 2021, 833 cases were reported under SMQ narrow Guillain-Barre syndrome (PTs: Acute motor axonal neuropathy; Acute motor-sensory axonal neuropathy; Bickerstaff's encephalitis; Chronic inflammatory demyelinating polyradiculoneuropathy; Demyelinating polyneuropathy; Guillain-Barre syndrome; Miller Fisher syndrome; Subacute inflammatory demyelinating polyneuropathy; Zika virus associated Guillain Barre syndrome).

Out of the 833 cases: 14 cases are literature reports; 8 cases were non-interventional/ post-marketing report; 810 cases were spontaneously reported and 1 case was from a study (D8110C00001).

Of the 833 cases, 828 (99.4 %) cases were serious and 443 (53.2 %) cases were reported by HCPs (medically confirmed). There were 11 (1.3%) cases with fatal outcome.

Of the 833 reports: 408 (49 %) were from the UK, 69 (8.3 %) were from Australia; 58(7,0 %) were from Germany; 51 (6.1 %) were from Spain; 46(5.5 %) were from Italy; 38 (4.6 %) were from France; 20 (2.4 %) were from India, 17 (2.0%) were from Brazil, 14 (1.7%) were reported each from Austria, Belgium and Portugal, 13 (1.6%) were reported from Mexico, 12 (1.4%) were reported from Netherlands, 11 (1.3%) were reported from Greece, 10 (1.2%) were reported from Sweden, 6 (0.7%) were reported from Ireland, 4 (0.5%) were reported from Finland, 3 (0.4%) were reported each from Bulgaria, Canada, Hungary, Norway and Poland, 1 (0.1%) was reported each from [redacted].

There were 370 (44.4 %) reports for female vaccinees, 438 (52.6 %) were for male vaccinees and the gender was not reported in 25 (3.0%) cases. The age range was 19-93 years of age: 532 (63.9 %) vaccinees were between age group of 18≤65 years of age; 219 (26.3 %) vaccinees were >65 years of age; in 7 (0.8%) vaccinees only age group was provided as adult and for 75 (9.0 %) the vaccinees the age was unknown.

The adverse event preferred terms reported included Guillain-Barre syndrome (788), Miller Fisher syndrome (31), Demyelinating polyneuropathy (17), Chronic inflammatory demyelinating polyradiculoneuropathy (10), Subacute inflammatory demyelinating polyneuropathy (5), Acute motor axonal neuropathy (5), Bickerstaff's encephalitis (1), Acute motor-sensory axonal neuropathy (1).

As requested by PRAC, these cases were reviewed for the pattern of GBS observed after vaccination with COVID-19 VACCINE ASTRAZENECA The pattern of GBS after vaccination is similar to other types of GBS. In the literature up to 50% of GBS cases either present with or have early predominance of facial diplegia as a clinical symptom (Fokke et al 2014, Hozumi A et al 1999 and Keane JR et al 1994). These reported cases reviewed from the AstraZeneca safety database do not have that high a percentage (50%) of facial diplegia. Because the cranial nerve (CN) involvement is not systematically queried or reported into the various health authorities, it is not possible to say exactly what percent of patients have either unilateral facial paralysis or facial diplegia. In the cases reviewed from AstraZeneca safety database, facial nerve involvement is not universally noted nor is it particularly rare, however determining a percent of cases with either unilateral or bilateral facial paralysis would not be possible due to the nature of spontaneous reporting.

Summary of cases with fatal outcome

Cumulatively, until 31 July 2021, 11 cases have been reported with fatal outcome under the SMQ narrow search for Guillain-Barre syndrome.

Of the 11 cases reported, 4 cases were from UK, 3 cases from Germany and 2 cases each were from Australia and Brazil. Eight out of 11 cases were reported in males, 2 in females and gender was not provided in one case. The age range was between 51-93 years. The narratives for the 11 cases with fatal outcome are provided in Appendix 10.

There was no information available if any of the 11 vaccinees had received second dose.

As per the neurology expert panel report, GBS has a recognized mortality of 3-5% in developed countries. The expected deaths from these 833 cases are therefore 25-42. The death rate as reported is low at only 1.3% as compared to the expected mortality rate.

Review of cases using BCC and causality assessment using WHO-UMC Criteria

The BCC (Law B 2021) criteria were used for the review of the data available in the case reports. Based on this approach, out of the 833 cases, 57 cases fulfilled level 1 criteria, 141 fulfilled level 2 criteria, 77 fulfilled level 3 criteria, 536 fulfilled level 4 criteria and 22 cases fulfilled level 5 criteria.

As requested by PRAC, the WHO-UMC causality assessment for the cases fulfilling BCC Level 1-3 is reassessed by safety physicians at AstraZeneca considering various factors of relevance like age, gender, TTO, comorbidities, concomitant medication, outcome, causality assessment, confounder disease or conditions.

In addition to the BCC, the published Brighton Case Definition for GBS (Law B 2021) 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). The risk factors are presented in Appendix 10.

Brighton Collaboration Criteria Level 1

Fifty-seven (57) out of the 833 case reports fulfilled BCC level 1 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory cerebrospinal fluid (CSF) and nerve conduction study (NCS) test results indicative of GBS.

20 reports were reported in females and 37 were reported in males and the age range was 31-80 years.

In 24 of the 57 cases, risk factors/ confounding factors and relevant co morbidities were provided. These cases are presented in Appendix 10. This information has been considered for the causality assessment according to WHO-UMC criteria. The risk factors/ confounding factors and relevant co morbidities included Breast cancer (2), Obesity(2), Progressive multifocal leukoencephalopathy (1), Lyme disease (1), Diabetes (3), Neuralgia (2), recent traffic accident/trauma (1), Type 1 diabetes mellitus/ with hyperglycaemia (1), Appendectomy (1), Autoimmune thyroiditis (1), colon cancer (1), Dyshidrotic eczema (1), Goitre (1), HIV and Lymphadenopathy (1), Irritable bowel syndrome (1), Malignant melanoma (1), multiple autoimmune disorders (1), Multiple sclerosis (1), Myasthenia gravis (1), Myelopathy (1) , Neuropathy peripheral/sensory (2), Pneumonia klebsiella (1), Prostate cancer (1), Renal failure (1), Restless legs syndrome (1) , Rheumatoid arthritis (1), Spinal stenosis (1), Steroid therapy for autoimmune dysfunction(1).

Increased likelihood of GBS is well accepted to occur as a paraneoplastic syndrome, after autoimmune disorders and after infections, including, but not limited to those of the respiratory and gastrointestinal (GI) tract such as Campylobacter and H. pylori from ulcer disease (Arellano LA et al 2014). However it is also documented in the literature and clinical practice that GBS has an increased risk of occurrence after non-infectious events, including

those that result in damage to the nervous system due to a variety of mechanisms. Some additional selected preceding disorders with an increased risk of GBS are noted here in response to the recent Health Authority/PRAC discussion on GBS and include sciatica (Brisby et al 2002, Yamauchi Y et al 1999), renal failure with neuropathy (Hamed SA et al 2019, Kitamura H et al 1988, Careless D et al 1993, Olbricht CJ et al 1993) and inflammatory bowel disease (Liu Z et al 2018).

An increased risk of GBS can also be associated with pre-existing nerve damage including from peripheral neuropathies. The causes of the preceding neuropathy may include but are not limited to toxicity (chemotherapy), inherited familial neuropathy, metabolic dysfunction and auto-immune disorders. Features in such disorders which are associated with increased risk or incidence of GBS frequently relate to a breakdown in the blood/nerve barrier, breakdown of the blood brain barrier, antibodies to gangliosides or ganglioside complexes, dysmyelination, other antibodies to axon surface markers and oligodendrocyte and Schwan cell antigens (Ang et al 2004, José et al 2002).

Out of these 57 cases, TTO from vaccination was beyond 42 days in one case and missing in 14 cases. The median TTO was 14 days.

In one case the event was reported to have occurred after receiving the second dose.

Out of the 57 cases fulfilling BCC Level 1, there were 31 that were assessed as conditional/ unclassified, 14 that were Unassessable/ unclassifiable and 12 that were assessed as unlikely using the WHO-UMC criteria for causality assessment. Out of these 57 cases, TTO from vaccination was beyond 42 days in one case and missing in 14 cases. The median TTO was 14 days.

These cases are tabulated in Appendix 10 .

Brighton Collaboration Criteria Level 2

One hundred forty-four (141) out of the 833 cases fulfilled BCC level 2. The cases fulfil this classification by the clinical course, examination findings and test results indicative of GBS based on either CSF findings or NCS. These cases are presented in Table 3 of Appendix 10.

Out of these 141 cases, 70 case reports were reported in males and 69 were reported in females, gender was unknown in 2 cases and the age range was –20-90 years.

In 66 of the 141 cases, risk factors/confounding factors, relevant comorbidities and concomitant medications were provided. These are presented in Appendix 10. This information has been considered for the causality assessment according to WHO-UMC criteria. The risk factors/confounding factors, relevant comorbidities and concomitant medications included Immunoglobulin therapy (for immune disorder)(6), Guillain-Barre

syndrome(5), Osteoarthritis (5), Influenza vaccine (6), Cerebrovascular accident (3), Suspected COVID-19 (3), hypoaesthesia (2), Neuropathy peripheral (2), Paraesthesia(2), Rheumatoid arthritis (2), Cholecystectomy (2), ANTI-D (RHO) Immunoglobulin Therapy(2), Appendectomy (2), Chronic kidney disease(2), Colitis ulcerative(2), Peripheral sensory neuropathy (1), Bell's palsy (1), Chronic inflammatory demyelinating polyradiculoneuropathy (1), Demyelinating polyneuropathy (1), Myelitis transverse (1), Nerve Pain (1), Autoimmune disorder (1), hereditary haemochromatosis (1),

Out of these 141 cases, the TTO from vaccination was beyond 42 days in 3 cases and missing in 35 cases. The median TTO was 15 days.

In 4 case reports, the event was reported to have occurred after receiving the second dose. One of these cases (Case ID: PPD) reported two episodes of Guillain-Barre syndrome, one with unknown time to onset considered after 1st dose and one with time to onset 10 days after receiving the 2nd dose. This patient also had an earlier prior episode of GBS after another non-COVID vaccine.

Out of the 141 cases fulfilling BCC level 2, 94 were assessed as conditional/ unclassified, 15 were assessed as unassessable/ unclassifiable and 32 were assessed as unlikely using the WHO-UMC criteria for causality assessment.

Out of these 141 cases, the TTO from vaccination was beyond 42 days in 3 cases and missing in 35 cases. The median TTO was 15 days.

Brighton Collaboration Criteria Level 3

Seventy-seven (77) out of 833 cases fulfilled BCC level 3. These case reports are level 3 based on clinical course, examination, and no additional plausible diagnosis; no NCS or CSF results. These cases are presented in Table 3 within Appendix 10.

Of the 77 case reports 43 were reported in females and 34 were reported in males, and the age range was 25-93 years of age.

In 46 of the 77 cases risk factors/confounding factors , relevant comorbidities and relevant concomitant medications were provided. These cases are presented in Appendix 10. This information has been considered for the causality assessment according to WHO-UMC criteria. The risk factors/confounding factors , relevant comorbidities and relevant concomitant medications included Immunoglobulin (6), Bell's palsy (3), Breast cancer (3), Guillain barre syndrome (3), hypothyroidism (3), Thyroidectomy (3), facial weakness (2), Influenza virus (2), Type 2 diabetes mellitus (1), Multiple sclerosis (1), Neuropathy (1), Paraesthesia (1), Acoustic neuroma (1), cerebellar stroke (1), cerebrovascular accident (1), stroke (1), Colon cancer (1), Goitre (1).

Out of these 77 cases the TTO from vaccination was missing in 19 cases. All cases had TTO within 42 days. The median TTO was 11.5 days.

One case reported the adverse event occurring after receiving the second dose.

Out of the 77 cases fulfilling BCC level 3, 44 cases were assessed as conditional/ unclassified, 21 were unlikely and 12 were unassessable/ unclassifiable using the WHO-UMC criteria for causality assessment.

Brighton Collaboration Criteria Level 4

Based on the review, 536 out of 833 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 case.

Brighton Collaboration Criteria Level 5

Based on the review, 22 out of 833 cases were classified as Brighton collaboration level 5 (ie, GBS excluded due to an alternative diagnosis).

Summary of review of cases

Of the 833 cases, only 443 (53.2 %) cases were reported by HCPs (medically confirmed).

Of the 833 cases, 275 cases met the BCC levels 1-3. Of these 275 cases, none of the cases were assessed to have a certain, possible or probable causality to COVID-19 VACCINE ASTRAZENECA and were assessed as Unlikely, Conditional or were Unassessable according to WHO-UMC classification.

Observed Versus Expected Analysis

The O/E Analysis for all cases of GBS is presented with different RWs (14 days, 30 days and 42 days) in Table 28. This included all reported cases irrespective of the BCC level. The RW of 42 days was included from the Brighton case definition (Sejvar et al 2011) and as recommended by the neurology expert panel. Additionally, RWs of 14 and 30 days were included as previously requested by PRAC. As per the recommendation from the neurology expert panel, the RW should be calculated between 5-42 days. To account for the mechanism by which GBS is caused, the lower limit of the window should be set conservatively at 5 days. Cases less than 5 days from vaccination would be questionable in any causative association and are therefore excluded from the counts of observed cases. This applies to all observed vs expected analyses presented here below.

The O/E analysis is highly dependent on background IRs used. For the calculations of the observed versus expected analysis, the background IR is referenced from the ACCESS protocol [2.035/100,000 person years (PY)]. However, a review of data generated by the Observational Health Data Science and Informatics (OHDSI) collaboration showed significantly higher estimates of background rates (Willame et al 2021).

Table 28 Observed Versus Expected Analysis for All GBS cases within 42 days

AEs	Risk window	BG rates	Exposure[a]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS All cases	14	2.035	220071905	361	171.66	2.1 (1.89 - 2.33)	Observed significantly > expected
GBS All cases	30	2.035	220071905	499	367.85	1.36 (1.24 - 1.48)	Observed significantly > expected
GBS All cases	42	2.035	220071905	518	514.99	1.01 (0.92 - 1.1)	Observed > expected

[a] Exposure until 31 July 2021.

Incidence rate (IR)=2.035/100,000 person years. Source: Willame et al 2021

CI Confidence Interval; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate; O Observed; TTO Time to onset.

An O/E analysis of cases meeting case definition according to the Brighton Criteria for Level 1, 2 or 3, based on clinical course, examination and no alternative aetiology in the presence or absence of NCS or CSF results are presented in Table 29 below.

Table 29 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 (Global reports) within 42 days

AEs	Risk window	BG rates	Exposure[a]	Observed number of case	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS cases BC Level 1-3	14	2.035	220071905	139	171.66	0.81 (0.68 - 0.96)	Observed significantly < expected
GBS cases BC Level 1-3	30	2.035	220071905	175	367.85	0.48 (0.41 - 0.55)	Observed significantly < expected
GBS cases BC Level 1-3	42	2.035	220071905	182	514.99	0.35 (0.3 - 0.41)	Observed significantly < expected

[a]Exposure until 31 July 2021.

Incidence rate (IR)=2.035/100,000 person years. Source: Willame et al 2021.

AEs Adverse Events, BC Brighton Criteria, CI Confidence Interval; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate; O Observed; TTO Time to onset.

Additionally, as per the PRAC request, the O/E analysis is presented with stratification by age for the European Economic Area (EEA), UK regions based on the available exposure data in Table 30. Cases with unknown time to onset were excluded from the analysis. The O/E analysis is also presented with stratification by age and gender Table 31 for UK region only based on the available exposure data.

Table 30 Observed Versus Expected Analysis for 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	14	1.86	26817010	23	19.12	1.2 (0.76 - 1.8)	Observed > expected
	30	1.86	26817010	33	40.97	0.81 (0.55 - 1.13)	Observed < expected
	42	1.86	26817010	35	57.36	0.61 (0.43 - 0.85)	Observed significantly < expected
Age 50 - 59	14	2.82	18968126	49	20.5	2.39 (1.77 - 3.16)	Observed significantly > expected
	30	2.82	18968126	60	43.94	1.37 (1.04 - 1.76)	Observed significantly > expected
	42	2.82	18968126	64	61.51	1.04 (0.8 - 1.33)	Observed > expected
Age 60 - 69	14	4.47	27572055	35	47.24	0.74 (0.52 - 1.03)	Observed < expected
	30	4.47	27572055	43	101.23	0.42 (0.31 - 0.57)	Observed significantly < expected

Table 30 Observed Versus Expected Analysis for 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
	42	4.47	27572055	43	141.72	0.3 (0.22 - 0.41)	Observed significantly < expected
Age 70 - 79	14	5.31	14415864	15	29.34	0.51 (0.29 - 0.84)	Observed significantly < expected
	30	5.31	14415864	16	62.87	0.25 (0.15 - 0.41)	Observed significantly < expected
	42	5.31	14415864	16	88.02	0.18 (0.1 - 0.3)	Observed significantly < expected
Age over 80	14	3.39	3620705	3	4.7	0.64 (0.13 - 1.87)	Observed < expected
	30	3.39	3620705	3	10.08	0.3 (0.06 - 0.87)	Observed significantly < expected
	42	3.39	3620705	3	14.11	0.21 (0.04 - 0.62)	Observed significantly < expected

Source: Willame et al 2021 (Median IR from UK CPRD, IT_ARS, ES_SIDIAP_PC).

Exposure until 31 July 2021 for EEA/UK.

CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; ES_SIDIAP_PC Spain Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (Spain Information System for the Development of Research in Primary Care), IR Incidence Rat, IT_ARS Italy Agenzia Regionale di Sanita Toscana (Regional Health Agency of Tuscany), O Observed; TTO Time to onset; UK United Kingdom.

The O/E analysis is presented with stratification by age and gender for UK region based on the available exposure data in Table 31. Since this represents data for UK only, it is not

comparable with Table 30 above which presents stratification by age group for EEA/UK region. The expected number of cases vary when presented by different age group for males and females due to different incident rates in these subgroups.

Table 31 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age and gender for UK only

Age group by Gender	Risk window	IR[a]/100,000 PY	Exposure [b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
	14	1.05	8446944	12	3.4	3.53 (1.82 - 6.17)	Observed significantly > expected
Female-Age 18 - 49	30	1.05	8446944	14	7.28	1.92 (1.05 - 3.23)	Observed significantly > expected
	42	1.05	8446944	15	10.2	1.47 (0.82 - 2.43)	Observed > expected
	14	2.28	6255395	17	5.47	3.11 (1.81 - 4.98)	Observed significantly > expected
Female-Age 50 - 59	30	2.28	6255395	20	11.71	1.71 (1.04 - 2.64)	Observed significantly > expected
	42	2.28	6255395	21	16.4	1.28 (0.79 - 1.96)	Observed > expected
	14	2.85	4742871	8	5.18	1.54 (0.67 - 3.04)	Observed > expected
Female-Age 60 - 69	30	2.85	4742871	9	11.1	0.81 (0.37 - 1.54)	Observed < expected
	42	2.85	4742871	9	15.54	0.58 (0.26 - 1.1)	Observed < expected
	14	3.61	3471390	8	4.8	1.67 (0.72 - 3.28)	Observed > expected
Female-Age 70 - 79	30	3.61	3471390	8	10.29	0.78 (0.34 - 1.53)	Observed < expected

Table 31 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age and gender for UK only

Age group by Gender	Risk window	IR[a]/100,000 PY	Exposure [b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
	42	3.61	3471390	8	14.41	0.56 (0.24 - 1.09)	Observed < expected
	14	1.98	1610970	1	1.22	0.82 (0.02 - 4.57)	Observed < expected
Female Age 80+	30	1.98	1610970	1	2.62	0.38 (0.01 - 2.13)	Observed < expected
	42	1.98	1610970	1	3.67	0.27 (0.01 - 1.52)	Observed < expected
	14	1.92	7790015	7	5.73	1.22 (0.49 - 2.52)	Observed > expected
Male-Age 18 - 49	30	1.92	7790015	12	12.29	0.98 (0.5 - 1.71)	Observed < expected
	42	1.92	7790015	13	17.2	0.76 (0.4 - 1.29)	Observed < expected
	14	3.29	6883876	19	8.68	2.19 (1.32 - 3.42)	Observed significantly > expected
Male-Age 50 - 59	30	3.29	6883876	21	18.6	1.13 (0.7 - 1.73)	Observed > expected
	42	3.29	6883876	24	26.04	0.92 (0.59 - 1.37)	Observed < expected
	14	7.9	4822169	18	14.6	1.23 (0.73 - 1.95)	Observed > expected
Male-Age 60 - 69	30	7.9	4822169	20	31.29	0.64 (0.39 - 0.99)	Observed significantly < expected
	42	7.9	4822169	20	43.81	0.46 (0.28 - 0.71)	Observed significantly < expected

Table 31 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age and gender for UK only

Age group by Gender	Risk window	IR[a]/100,000 PY	Exposure [b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
	14	7.44	3128463	5	8.92	0.56 (0.18 - 1.31)	Observed < expected
Male-Age 70 - 79	30	7.44	3128463	5	19.12	0.26 (0.08 - 0.61)	Observed significantly < expected
	42	7.44	3128463	5	26.77	0.19 (0.06 - 0.44)	Observed significantly < expected
	14	5.45	956739	1	2	0.5 (0.01 - 2.79)	Observed < expected
Male-Age over 80	30	5.45	956739	1	4.28	0.23 (0.01 - 1.3)	Observed < expected
	42	5.45	956739	1	6	0.17 (0 - 0.93)	Observed significantly < expected

Source: Willame et al 2021 (Median IR from UK CPRD, IT_ARS, ES_SIDIAP_PC) Exposure until 31 May 2021 for UK.

CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate, IT_ARS Italy Agenzia Regionale di Sanita Toscana, O Observed; PY Person Years, TTO Time to onset, UK United Kingdom.

Reporting Rate for Guillain-Barré Syndrome (GBS)

Cumulative reporting rate for Guillain-Barré syndrome based on data from UK, EEA and Global are provided in Table 32 here below, as requested by PRAC in 5th Assessment Report from the monthly safety summary report.

Table 32 Cumulative reporting rate for Guillain-Barré syndrome based on data from UK, EEA and Global

Region	Total exposed (in million)	Observed cases with RW 42 days	Observed cases with RW 42 days by BC 1, 2 , 3	Reporting rate per million for all cases	Reporting rate per million for all BC 1, 2 and 3 cases	Background rate (per million)	Rate relative to Background (per million)	Rate relative to Background (per million) for BC1, 2, and 3 cases
UK	48358491	361	139	7.47	2.87	2.3	5.17	0.57
EEA	65995227	499	175	7.56	2.65	2.3	5.26	0.35
Global	220071905	518	182	2.35	0.83	2.3	0.05	-1.47

For GBS per 1M from Truven Market Scan-2019
EEA European Economic Area, RW Risk Window, UK United Kingdom.

The overall rate relative to background rate in the UK and EEA were 5.17 and 5.26, respectively. However, when the number of observed cases is stratified by BC levels 1-3 with RW of 42 days, the rate relative to background rates reduces to 0.57 and -0.35. For global cases the rate relative to background rate is 0.05 for all observed cases with RW 42 days. When only cases that fulfil BC 1-3 are included, the rate relative to background rate reduces to -1.47.

Summary of O/E Analysis

The O/E 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 (Table 28). However, an O/E analysis of cases meeting the BCC Level 1, 2 or 3 (Table 30) with TTO within 14 days, 30 days and 42 days from vaccination showed that the observed number of GBS cases were fewer than the number of expected cases.

When cases from EEA and UK, or UK alone are analysed according to age group and sex, as well as 14, 30 and 42 days windows (Table 29, Table 30), numbers of cases become very small resulting in some categories where observed is greater and in some less than expected. Also, there is too much variability in these data to make an assessment on causal association. As discussed in the neurology expert panel report (see below), these categories lack consistency, coherence and plausibility within the understanding of GBS.

Summary of neurology expert panel report for data cut off until 31 July 2021.

AstraZeneca convened a panel of independent expert Neurologists [PPD] to review data on GBS cases with a

data cut off of 31 July 2021 to assess any possible link of GBS to the COVID vaccination with AstraZeneca vaccine.

Guillain-Barre syndrome is an immunological (usually post infectious) inflammatory polyradiculoneuropathy with circumscribed but somewhat variable clinical features, known supportive investigations and a pathogenesis which is better understood than most autoimmune disease. GBS occurs at a rate of about 2 per 100000 of the population per year, affecting both sexes and all ages. Cases of Guillain-Barre syndrome have been described after COVID-19 vaccination. Cases of GBS will occur by chance in the huge population of vaccinees in a mass vaccination campaign.

Cases reported to the UK Yellow Card system are high sensitivity and low specificity, with a tendency to over-reporting bias. This also applies when using the MedDRA search strategy in AstraZeneca global safety database to retrieve cases using the SMQ narrow Guillain-Barre syndrome. To note, overall only about 50% of the cases were medically confirmed. Out of 408 cases of GBS reported cumulatively in the UK, 158 (38.7%) were medically confirmed. The National Health Service (NHS) England IVIG database mandates the recording of every hospitalised UK patient being treated with IVIG, and has high specificity for GBS as cases are reviewed and Hospital Trusts are only paid for their IVIG on reporting data. It collects approximately 90% of UK GBS (almost all treated with IVIG) and has done so for more than 5 years, providing control data, with GBS incidence correlating exactly with international GBS incidence [Keddie et al 2020, Sejvar et al 2011]. This data source has lower sensitivity and a tendency to under-reporting bias, but its substantial specificity along with control data from previous years mitigate this.

The data from the safety database searches for all GBS reported after COVID-19 VACCINE ASTRAZENECA vaccination suggest a greater observed than expected number of GBS cases at 14 or 30 days from COVID vaccination, but this is not found to be significant within the accepted 42 day window for vaccine associated GBS. When only cases with clinical diagnostic clarity (even without laboratory support), that is BCC Level 1-3 are analysed observed cases are significantly fewer than expected, and this is a more certain result.

When cases from EEA and UK, or UK alone are analysed according to age group and sex, as well as 14, 30 and 42 days windows, numbers of cases become very small.. These categories lack consistency, coherence and plausibility within the understanding of GBS. These data are therefore of uncertain meaning and security.

The UK has the only rapidly up to date, national system (NHS England IVIG database) of recording GBS facilitated by the unidimensional treatment of almost all hospitalised GBS in the UK and mandatory reporting with financial penalties for late deposition of data. In 2020 cases of GBS had reduced during the COVID pandemic because of social distancing and hygiene regulations [Keddie et al 2020]. In 2021 the total number of cases of hospitalised

IVIG treated GBS from January to May does not exceed the UK 5 month average, even though greater numbers of GBS were recorded in March and April. However it is unclear why, if the March and April increase in numbers relates to vaccination why it began well after the 42 day window and has not continued into May and June with ongoing vaccination. Thus there is no obvious coherence for an association in the monthly data and they lack consistency with the suggestion of a significant increase in GBS numbers suggested by the safety database SMQ 'all-GBS' figures.

The neurology expert panel proposed that the cautionary wording in the EU SmPC on GBS remains, but that causation is not confirmed by the data available to date for the AstraZeneca COVID-19 vaccination.

Summary and conclusion:

Of the 833 cases reported, only 443 (53.2 %) cases were reported by HCPs (medically confirmed). A total of only 275 cases met the BCC Level 1-3 of diagnostic certainty and none of these cases were considered to be certainly/possibly/probably related to COVID-19 VACCINE ASTRAZENECA based on the WHO-UMC classification for causality assessment. The quantitative review shows greater observed than expected number for all GBS cases at 14 or 30 days from COVID vaccination, but this is not found to be significant within the accepted 42 day window for vaccine associated GBS. When only cases with clinical diagnostic clarity (BCC Level 1-3) are analysed observed cases are significantly fewer than expected. When cases from EEA and UK, or UK alone are analysed according to age group and sex, as well as 14, 30 and 42 days windows, the numbers of cases become very small resulting in some categories where observed is greater and in some less than expected. Also, there is too much variability in these data to make an assessment on causal association.

Based on a review of currently available information, it is the continued opinion of AstraZeneca that a reasonable possibility of a causal relationship between COVID-19 VACCINE ASTRAZENECA and GBS has not been established at this time.

The section 4.4 (Special warnings and special precautions for use) of the CDS for COVID-19 VACCINE ASTRAZENECA includes precautionary text on neurological events stating that very rare events of demyelinating disorders have been reported following vaccination with COVID-19 VACCINE ASTRAZENECA.

Guillain-Barré Syndrome 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 Acute disseminated encephalomyelitis (ADEM)

Search Strategy

A search of the global patient safety database was conducted for cumulative adverse event data (up to 28 June 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.

Review of Cases

The search identified 26 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. All 26 were spontaneously reported, no cases were from other sources such as literature, solicited or clinical.

Of the 26 cases, 26 (100.0%) cases were serious and 20 (76.9%) cases were reported by HCPs (medically confirmed). There were no cases with a fatal outcome.

Of the 26 reports: 9 (34.6%) were from the UK, 5 (19.2%) were from Spain; 2 (7.7%) cases each were reported from France and Germany; 1 case report each were reported from [redacted].

There were 15 (57.7%) case reports for female vaccinees and 11 (42.3%) were for male vaccinees. The age range was 29-83 years of age: 20 (76.9%) vaccinees were between age group of 18≤65 years of age; 4 (15.4%) vaccinees were >65 years of age; for 2 (7.7%) the vaccinees the age was unknown.

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 26 cases: 0 cases fulfilled level 1 criteria; 4 cases fulfilled level 2 criteria; 5 cases fulfilled level 3 criteria; 9 cases fulfilled level 4 criteria; 8 cases fulfilled level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for GBS (Law B 2021) 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 Level 1

None out of 26 case reports fulfilled Brighton collaboration level 1 criteria according to classification by clinical course, examination features and/or level of certainty.

Brighton Collaboration Level 2

4 out of 26 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 38, Page 88 of the June 2021 MSSR.

Three reports were reported in females and one was reported in mles and the age range was 37-47 years. The risk factors/confounding factors in these cases included anxiety, depression, psoriasis, hypertension and suspected COVID-19. Out of these 4 cases, the time to onset from vaccination was missing in one case. The median time to onset was 8 days. In all of the cases there were alternative causal factors noted.

Brighton Collaboration Level 3

Five (5) out of 25 case reports fulfilled Brighton collaboration level 3 criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory and are presented in Table 39, Page 90 of the June 2021 MSSR.

Three (3) reports were reported in females and 2 were reported in males and the age range was 45 - 66 years. The risk factors/confounding factors in these cases included hypothyroidism, type 2 diabetes mellitus, hypertriglyceridaemia, hypovitaminosis, chronic hepatitis C, schizophrenia, hypertension and colitis ulcerative. Time to onset was missing for all five cases. In most of the cases there were alternative causal factors noted.

Brighton Collaboration Level 4

Nine (9) out of 25 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

Eight (8) out of 25 case reports fulfilled Brighton collaboration level 5 criteria, (ie, ADEM (excluded due to an alternative diagnosis).

Observed versus expected analysis

The O/E Analysis for all cases of ADEM is presented with different RWs (14 days, 30 days and 42 days) in Table 40, Page 91 in the June 2021 MSSR. This included all reported cases irrespective of the Brighton criteria level. The RW of 2-42 days was included from the Brighton case definition (Law B 2021). 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.

Acute Disseminated Encephalomyelitis is rare and specific events that can only be seen with ICD-9/10CM codes were only observed in 5 data sources with rates < 1/100,000 person-years. Number of incident events over the study period according to the narrow definition for ADEM was more in the Aarhus University (DCE-AU) data source, also this data source was used by PRAC in the earlier MSSR assessment reports. Hence IR from DCE-AU was used for ADEM O/E analysis (Willame et al 2021). In the previous MSSR, median IR (2017-2019) ACCESS Background rates of adverse events of special interest (AESIs) for COVID-19 vaccines: ADEM-Narrow was used and did not include IR from DCE-AU.

An O/E 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 aetiology (Law B 2021) are presented in Table 41, Page 93 of the June 2021 MSSR.

Additionally, as per the PRAC request, the O/E analysis is presented with stratification by age for the EEA, UK regions based on the available exposure data, this is presented in Table 42, Page 92 of the June 2021 MSSR (page 92). Incidence rates were obtained from Aarhus University Hospital (AUH) in Denmark, which is a robust database where Staten Serum Institute (SSI) has direct access via *ad-hoc* linkage, which has led to several interventions to improve registration of vaccinations, including the compulsory registrations of vaccinations since 2015 (Willame et al 2021). This is also the IR suggested by PRAC in the 4th assessment report for the monthly safety summary report.

An O/E analysis of cases meeting case definition according to Brighton Criteria for Level 1, 2 or 3 was presented in Table 43, Page 94 of the June 2021 MSSR (page 94).

Summary

The O/E analysis of cases of ADEM suggested that expected cases were more than observed in all stratifications, apart from ADEM overall with RW 14 days and IR from ACCESS protocol is used.

However, an O/E analysis of cases meeting BCC levels 1-3 showed that the observed number ADEM cases fulfilling case definition were less than number of expected cases in all RWs, ie, 14, 30 and 42.

Observed versus expected analyses are highly dependent on the IRs used. For calculations of O/E analysis, the IRs referenced are from Willame et al 2021.

When O/E analyses are stratified by age, all age groups have observed cases few than expected, apart from in age group 18-49 years and 14 day RW (refer: June 2021 MSSR Table 42, Page 92). The IR used is from AUH/SSI as suggested by PRAC.

The O/E analysis for cases meeting the Brighton Criteria for Level 1, 2 or 3 and stratified by age group with different RWs (14, 30 and 42 days) suggested that the observed cases occurred less frequently than expected in all age groups (refer: June 2021 MSSR Table 43, Page 94).

Further review of cases in these groups where observed were above expected showed that the majority of cases had insufficient information to make any causality assessment.

Literature review

A literature search was conducted in the Embase and InsightMeme database to review the occurrence of ADEM in association with vaccines, other COVID Vaccines and COVID-19 infection using the key terms 'COVID 19 vaccines', 'encephalitis'.

Acute Disseminated Encephalomyelitis is a condition characterized by inflammation and damage to myelin chains in the brain (encephalon) and spinal cord (medulla). The fact that the condition is disseminated means that it is widespread and can cause symptoms and signs in many places in the body. Acute Disseminated Encephalomyelitis is usually preceded by a viral disease, an upper respiratory tract infection or vaccination, the condition probably occurs as a result of a transient autoimmune reaction, that is, the body's defense system incorrectly attacks its own tissue. The disease usually starts quickly and can cause a variety of symptoms (Akutt disseminert encefalomyelitt (ADEM), 2018).

Though rare, mild and severe neurological side effects have been occasionally reported with SARS-CoV-2 vaccines. According to the Food and Drug Administration (FDA)/ Centres for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS), 9442 reports of adverse reactions in association with the use of with SARS-CoV-2 vaccines have been submitted to VAERS as of 02 March 2021. The most common neurological symptoms included dizziness, headache, pain, muscle spasms, myalgia and paresthesias, which are expected to occur as acute, transient effects of the vaccination. Rare cases of tremor, diplopia, tinnitus, dysphonia, seizures and reactivation of herpes zoster have been also reported. There were also cases of stroke (n = 17), GBS (n = 32), facial palsy (n = 190), transverse myelitis (n = 9) and ADEM (n = 6) in the VAERS database (Finsterer et al 2021). Furthermore, ADEM is a disease which has been associated with several vaccines such as rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, and the Hog vaccine.

In the literature (Yu et al 2020), since COVID-19 outbreak in January 2020, several, pieces of evidence suggest an association between ADEM and SARS-CoV-2. The first case of COVID-

19–related ADEM was reported in a PPD-year-old PPD, and MRI revealed PPD A PPD-year-old PPD developed a PPD and impaired PPD response weeks after a SARS-CoV-2 infection. PPD MRI demonstrated PPD and the clinical examination and CSF analysis were consistent with an PPD. Furthermore, the autopsy of a PPD-year-old patient diagnosed with COVID-19 showed scattered clusters of macrophages, axonal injury, and a perivascular ADEM-like appearance in the subcortical white matter (Yu et al 2020).

The literature analysed show a clear association between the pathologies, with SARS-CoV-2 potentially triggering ADEM. However, the review of literature did not identify any definitive causal association between ADEM and COVID Vaccines.

Conclusions

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 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.

16.3.1.1.3 Encephalitis

Search Strategy

A search of the global patient safety database was conducted for cumulative adverse event data (up to 28 June 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using PTs under SMQ narrow Noninfective Encephalitis (excluding ADEM, which is discussed above) and HLT Encephalopathy in association with the use of COVID-19 VACCINE ASTRAZENECA.

Review of Cases

The search identified 136 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 136 cases, 135 cases were spontaneously reported and 1 case is from study ICMR/SII-AZD-COVID-19/2020, that case is described below under clinical trials. No cases were post-marketing solicited reports or literature.

Of the 136 cases, 134 (98.5%) cases were serious and 83 (61%) cases were reported by HCPs (medically confirmed). There were 5 cases with fatal outcome.

Out of the 136 reports, 55 (40.4%) were from the UK, 12 (8.8%) cases each were reported from France, Germany, Italy and Spain, 6 (4.4%) cases were reported from Australia, 3 (2.2%) cases each from Belgium, Netherlands and India, 2 (1.5%) cases each from Brazil,

Hungary and Romania and 1 (0.7%) report each from [redacted]

There were 67 (49.3%) reports for female vaccinees, 68 (50.0%) were for male vaccinees and the gender was not reported in 1 (0.7%) cases. The age range was 18-96 years of age; 90 (66.2%) vaccinees were between age group of 18-<65 years of age, 37 (27.2%) vaccinees were >65 years of age and for 44 (9.8%) vaccinees the age was unknown.

In 2 case reports, the events were reported to have occurred after the second dose of vaccine.

The adverse event preferred terms reported included Encephalitis (72), Encephalopathy (22), Encephalitis autoimmune (9), Encephalomyelitis (8), Noninfective encephalitis (8), Autoimmune encephalopathy (5), Hypoxic-ischaemic encephalopathy (3), Limbic encephalitis (3), Posterior reversible encephalopathy syndrome (3), Noninfective encephalomyelitis (2), Encephalitis brain stem (1), Encephalitis post immunization (1), Immune-mediated encephalitis (1), Opsoclonus myoclonus (1), Postresuscitation encephalopathy (1) and 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 136 cases, 1 cases fulfilled level 1 criteria, 2 fulfilled level 2 criteria, 24 fulfilled level 3 criteria, 56 fulfilled level 4 criteria and 53 cases fulfilled level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for Encephalitis (Law B 2021) 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 136 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). No case report fulfilled this classification.

Brighton Collaboration Level 2

Three (3) out of the 136 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). These cases are summarised in Table 44 of the June safety summary report (page 98).

Two subjects were PPD aged PPD years and PPD years and one was a PPD of unknown age.

Risk factors reported were L-Thyroxine for hypothyroidism and deep vein thrombosis (suggestive of vascular disease).

Time to onset was 7 days for one report, for the other two the time to onset was unknown.

The reports had limited information to make causality assessment or alternative causal factors were noted.

Brighton Collaboration Level 3

Twenty-four (24) out of 136 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). The cases are summarised in Table 45 of the June safety summary report (page 99).

Sixteen (16) 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 24 cases, the TTO from vaccination was missing in 4 cases. The median TTO was 9 days. In most of the cases there was limited information to make any causality assessment or presence of confounding factors.

Brighton Collaboration Level 4

Based on the review, 56 out of 136 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 case.

Brighton Collaboration 5

Based on the review, 53 out of 136 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.

Observed versus expected analysis

The O/E analysis for all cases of encephalitis is presented with different RWs (14 days, 30 days and 42 days) in Table 46, Page 103 of the June 2021 MSSR. This includes all reported cases irrespective of the BCC level. The RW of 2-42 days was included from the Brighton case definition (Law B 2021). 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 IRs used are from Willame et al 2021 and from Granerod et al 2013.

An O/E 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) are presented in Table 47, Page 104 of the June 2021 MSSR.

Additionally, as per the PRAC request, the O/E analysis is presented with stratification by age for the EEA, UK regions based on the available exposure data, this is presented in Table 48, Page 105 of the June 2021 MSSR.

Summary

The O/E analysis of cases of encephalitis showed that observed cases occurred significantly less frequently than expected for all stratifications, except for encephalitis – in 18-49 age group with data from EEA/UK and RW of 14 days where observed cases (30) was greater than expected (29 cases). However, on further review of cases in 18-49 years from EEA/UK showed that the majority of cases had insufficient information to make any causality assessment and only 7 cases met the BCC Level 1, 2 or 3. O/E analysis for cases of encephalitis in this age group based on BCC Level 1, 2 or 3 showed that observed cases occurred significantly less frequently than expected.

Literature review

A literature search 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 using the key terms ‘COVID 19 vaccines’, ‘encephalitis’.

The review of literature did not identify any definitive causal association between encephalitis and COVID-19 Vaccine AstraZeneca.

Conclusions

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.

16.3.1.1.4 Bell's Palsy / Facial paralysis

As part of a request from PRAC regarding unilateral facial weakness and to identify case of isolated CN VII palsies, the AstraZeneca global safety database was searched using the MedDRA (v24.0) PTs of the AESI concept of Bell's Palsy, including PTs Facial paralysis, Facial paresis and Bell's palsy reported with COVID-19 VACCINE ASTRAZENECA cumulative until 28 June 2021. Using this search strategy, a total of 1228 cases of Bell's palsy were identified. Of these 1228 cases, 1189 cases were processed and 39 were not yet processed. Ten (10) cases were from non-interventional post-marketing studies, 1215 were spontaneously reported and 3 cases were from literature. Cases indicating facial weakness/paralysis occurring as a feature of another process were excluded (ie, co-reported PTs associated with pain, abnormal sensation, hearing/vision disturbances or loss, and/or swallowing difficulties. Preferred term's related to new-onset stroke, transient ischemic attack, and cerebral and/or intracranial pathology, which had accompanying CN VIII disfunction were also excluded. Cases of Bell's palsy or facial weakness/paralysis with past medical histories of transient ischemic attack or stroke were included in the analysis. Narratives for cases were further reviewed to ascertain the accuracy of the described inclusion/exclusion criteria and classified according to BCC.

After exclusion of the above mentioned cases, a total of 188 cases of 'pure' closed Bell's palsy cases were identified that involved both Bell's palsy and facial paralysis and were independently included in each review of the cases below.

Of the 188 cases of Bell's palsy that were included in the analysis, 87 (46.3%) were reported in females and 95 (50.5%) were reported in males. Gender was not reported in the remaining 6 (3.2%) of reports. Age ranged from 18 years to <65 years in 113 (60.1%) of the reports and 65+ years in 57 (30.3%). Age was not reported in 16 (8.5%) of the reports. 2 reports (1.1%) were reported in "Adult" without further age definition. Age was reported in the 188 reports considered pure Bell's palsy with age ranging from 21 – 89 years and a median of 59 years. Eighty-six (45.7%) were not medically confirmed, with the remaining 102 (54.3%) being medically confirmed.

Of the 188 cases, a total of 227 events of PTs Bell's palsy, Facial paralysis or Facial paresis considered pure Bell's palsy were identified. Of these 227 events, 154 (67.8%) were considered serious. There were no events of pure Bell's palsy with fatal outcome reported. Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA to Bell's palsy was available in 173 of the 227 events. Two events were reported to have occurred after receiving the second dose of vaccine. Thirty-eight (22.0%) of the events occurred within 1 day of vaccination, 50 events (28.9%) occurred 2 – 7 days after vaccination, 22 (12.7%) occurred 8 – 14 days after vaccination, and the remaining 63 events (36.4%) occurred >14 days after vaccination. Outcome was reported in 176 of the 227 events considered pure Bell's palsy with 87 (46.3%) reported as Not recovered, 1 (0.6%) as Recovered with sequelae, 54 (30.7%) as Recovering and 34 (19.3%) as Recovered. This distribution of outcome was similar for both serious and non-serious cases when analysed separately.

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 188 cases of 'pure' Bell's palsy, no case fulfilled level 1 criteria, 2 cases fulfilled level 2 criteria, no case fulfilled level 3 criteria, 140 fulfilled level 4 criteria and 46 cases fulfilled level 5 criteria.

Brighton Collaboration Levels 1-3

One out of the 181 case reports fulfilled Brighton collaboration level 2 criteria and one fulfilled level 3. The cases fulfil this classification by clinical course such as ability to wrinkle forehead or raise eyebrows, abrupt and/or rapidly progressed onset and/or complete or partial resolution and/or laboratory or radiology investigations (Law B 2021).

No cases fulfilled BCC level.

The case report fulfilling Brighton collaboration level 2 was a PPD -year-old PPD from the PPD who experienced event of PPD 8 days after receiving the second dose of vaccine. Medical history included PPD and elevated BP from time to time, however, not requiring medication. Symptoms included PPD The case report was considered serious due to hospitalisation. No reasonable alternative causal factors were noted and causal association with COVID-19 VACCINE ASTRAZENECA cannot be ruled out.

One case report fulfilling Brighton collaboration level 3 was a PPD -year-old PPD from the PPD who experienced the events of PPD . Time to onset for PPD was 6 days, for PPD 19 days and for PPD the time to onset was 20 days. The events occurred after receiving the first dose of COVID-19 Vaccine. The case report had limited information to make any causality assessment.

Brighton Collaboration Levels 4-5

Based on the review, 140 out of 188 pure Bell's Palsy 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 case.

Forty-six (46) cases fulfilled Brighton collaboration level 5 criteria (ie, Bell's Palsy excluded due to an alternative diagnosis).

Overall, the age and gender distribution in the 188 cases is consistent with the recognized risk factors for Bell's Palsy.

Out of the total of 1228 cases reported these three PTs, 188 were considered pure Bell's Palsy after exclusion of co-reported PTs. Of the 188 cases, two cases fulfilled case definition by fulfilling Brighton collaboration levels 1-3. One case had a history of intermittent hypertension and pending work up without details. One case had no work up.

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.

Summary

The O/E analysis for all reported cases of Bell's palsy showed that observed cases occurred significantly less frequently than expected (refer: June 2021 MSSR Table 50, Page 110). Cases with unknown time to onset are not included unless otherwise stated.

Conclusion

The O/E analysis with RW 42 days suggests that expected cases are more than observed cases. If cases fulfilling BCC level 1, 2 or 3 are analysed the observed number of cases would be 2 cases versus 2568.61 expected cases, respectively.

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 AESI Bell's Palsy including PTs facial paralysis, facial paralysis and Bell's Palsy, 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.

16.3.1.1.5 Trigeminal Neuralgia

At the request of the EU PRAC and based on the WHO-UMC signal of trigeminal neuralgia with COVID-19 vaccines, AstraZeneca has provided a cumulative review of trigeminal neuralgia using the HLT: Trigeminal disorders below. As this review was requested for inclusion in this PBRER, it has not been assessed through any procedure previously.

Search Strategy

A search of the global patient safety database was conducted for cumulative adverse event data (up to 28 June 2021) from all sources (clinical, spontaneous, solicited reporting and literature) using all PTs under the HLT: Trigeminal disorders.

Review of Cases

The search identified 231 case reports in vaccinees who received COVID-19 VACCINE ASTRAZENECA. Out of the 231 cases, 225 cases were spontaneously reported, and 6 cases were post-marketing solicited reports.

Of the 231 cases, 176 (76.2%) cases were serious and 55 (23.8%) non serious. Forty-three (18.6%) cases were reported by HCPs (medically confirmed). There were 0 cases with fatal outcome.

Out of the 231 reports, 149 (64.5%) were from the UK, 16 (6.9%) each from France and Italy, 6 (2.6%) from Spain, 5 (2.2%) from Netherlands, 4 (1.7%) each from Australia, Austria, Germany, Norway, and Poland, 3 (1.3%) from Bulgaria, 2 (0.9%) each from Canada, Finland, Ireland, and Portugal, and 1 (0.4%) each from [redacted]

The 231 reports contained 249 relevant events. The adverse event preferred terms reported are shown in Table 33.

Table 33 Trigeminal Neuralgia PTs

Preferred Term	#Events
Trigeminal neuralgia	130
Facial neuralgia	57
Ophthalmic herpes zoster	36
Trigeminal nerve disorder	13
Numb chin syndrome	6
Trigeminal neuritis	3
Trigeminal palsy	2
Vth nerve injury	1
Trigeminal nerve paresis	1
Grand Total	**249**

PT Preferred Term.

An individual case report can have more than one of the above events reported.

There were 178 (77.1%) reports for female vaccinees, 47 (20.3%) were for male vaccinees and the gender was not reported in 6 (2.6%) cases. With regards to age, 173 (74.9%) vaccinees were between age group of 18-<65 years of age, 35 (15.2%) vaccinees were >65 years of age and for 21 (9.1%) vaccinees the age was unknown.

Of the 231 reports, on review, 60 were not possible to confirm as true cases of trigeminal neuralgia. These case included cases of: Ophthalmic herpes zoster (36), Numb chin syndrome (6), Limited information on the event (5), Fibromyalgia (4), Pain radiating to other parts (1), Bell's palsy (1), Aching joints and limbs (1), Trigeminal disorder (1), Facial droop (1), Trigeminal palsy (1), Covid-19 diagnosis (1), Gum blisters (1), Case with no pain involved (1). These cases are not further discussed, leaving 171 remaining.

Out of 171 cases, in 166 the events were reported to have occurred after the 1st dose of vaccine. In 4, the events occurred after 2nd dose, and in 1 case the events occurred after both doses.

Time to onset for the 171 cases is presented below in Table 34:

Table 34 Time to Onset for Trigeminal Neuralgia Cases

Time to Onset	#Cases
1 hour	1
<1 day	1
0 day	33
1 day	32
2 days	10
3 days	12
4 days	5
5 days	5
6 days	7
8 days	4
10 days	2
11 days	2
12 days	3
13 days	1
14 days	2
17 days	2
21 days	1
23 days	1
26 days	1

Table 34 Time to Onset for Trigeminal Neuralgia Cases

Time to Onset	#Cases
35 days	1
39 days	1
77 days	1
81 days	1
Cannot determine.	2
Not stated.	40
Grand Total	**171**

Where data on time to onset were available (129 cases), most cases (69%) occurred with an onset 3 days or less after vaccination, with 51.9% occurring at 1 day or less. However, only 8 of the cases with an onset of 3 days or less were considered on review to have no reasonable alternative causal factors noted and causal association with COVID-19 VACCINE ASTRAZENECA was unable to be ruled out. Only 1 of these 8 cases was medically confirmed. These 8 cases are presented later in this report.

Of the 171 cases, 82 contained limited information, precluding a more thorough assessment.

Of the remaining cases, 81 were confounded by medical history, including: History of trigeminal neuralgia, suspected COVID-19, osteoporosis, multiple sclerosis, facial neuralgia, migraine, trigeminal neuralgia, hypertension, occipital neuralgia, acute allergy after vaccination, allergic reaction to bee sting, Crohn's disease, neuralgia, hypertension, diabetes, spondylitis, breast cancer, menopause, cervical pain, multiple sclerosis, chest pain, allergy, headache, depression, anxiety, diabetes, “electric pain”, epilepsy, lymes disease, eye strain, facial herpes, pain, osteoporosis, neurofibromatosis, shingles, head pain, stress, coeliac disease, heart attack, temporal arteritis, herpes on lip, Behcet's syndrome, nerve pain, stroke, psoriatic arthritis, vitamin deficiency, and inflammation. Some cases contained multiple confounding factors.

A summary of the causal assessments made after review of the cases is provided in Table 35:

Table 35 Causal Assessments for Trigeminal Neuralgia Cases

Assessment	#Cases
Alternative causal factors noted.	81
Limited information to make any causality assessment.	82
No reasonable alternative causal factors were noted and causal association with COVID-19 VACCINE ASTRAZENECA cannot be ruled out.	8

Table 35 Causal Assessments for Trigeminal Neuralgia Cases

Assessment	#Cases
Grand Total	**171**

For the 8 cases where no reasonable alternative causal factors were noted and causal association with COVID-19 VACCINE ASTRAZENECA could not be ruled out, summaries are provided below. One was medically confirmed. The 8 cases described events of Trigeminal neuralgia (5), Facial neuralgia (2), and Trigeminal nerve disorder (1), occurring 0-3 days after vaccination. In these 8 cases, outcome was ongoing in 2, recovered or recovering in 6. Treatment for the event was reported in 2 cases (paracetamol, and amitriptyline). One case was confounded by concurrent ear infection. In these cases, the events occurred the same day as vaccination in 1 case, after 1 day in 5 cases, after 2 days in 1 case, and after 3 days in 1 case. Age ranged from 29-60 years, and all 8 cases were in PPD

PPD (PPD) concerned a PPD year old PPD. The patient's past and current medical history included asthma, urinary tract infection (UTI), single functional kidney, kidney infection and bleeding urinary tract. No concomitant products were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On PPD, 1 day after vaccination, the patient experienced seizure (febrile) UTI, elevated heart rate from 128-154, PPD, unfit for work, temperature of 39.5 to 40.5, nerve pain down face and head, neurological pain along face, severe, continuous headache, loss of appetite, and zero energy. The patient recovered from the events of unfit for work, nerve pain down face and head, neurological pain along face like nerve pain and severe, continuous headache on an unspecified date. The patient recovered from the event(s) of temp of 39.5 to 40.5 after 5 days on an unspecified date. At the time of reporting, the events of seizure (febrile), UTI, elevated heart rate from 128-154, uncontrollable shaking, loss of appetite and zero energy was ongoing.

PPD (PPD): concerned a PPD year old PPD patient. The patient's past and current medical history included asthma and anaphylactic reaction. No concomitant products were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On PPD, 2 days after vaccination, the patient experienced PPD pain through PPD side of face through teeth & into ear. At the time of reporting, the event was ongoing.

PPD (PPD) concerned a PPD year old PPD patient The patient's past and current medical history included asthma. No concomitant products were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On the same day of vaccination, the patient experienced PPD. Description of the event was as follows: Started with pain on PPD side of face in an E formation stemming from just above

the ear near the temple. This began during the early evening after the vaccine and dissipated during the early hours of PPD .

PPD (PPD): concerned a PPD year old PPD patient. Past and current medical history included allergy to nuts (ongoing). No concomitant products were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD . On PPD , the same day as vaccination, the patient experienced PPD , numbness in vaccination arm, numbness in face, PPD , visual disturbance, BP decreased, PPD , feeling of unintentional intravascular injection, injection site hematoma with bleeding, chest pain, injection site paresthesia, and headache. On PPD , the patient experienced PPD , was PPD , dyspnoea, fever, and chills. The patient recovered from the event of PPD on an unspecified date. At the time of reporting, the events of BP decreased, fever and headache were ongoing. At the time of reporting, the other events were improving.

PPD (PPD) concerned a PPD year old PPD patient. The patient's past and current medical history included PPD , bone marrow cancer, and allergy to antibiotic PPD . Concomitant medication included PPD The patient received COVID-19 Vaccine AstraZeneca on PPD On PPD , 1 day after the vaccination, the patient experienced onset of migraine, especially in correspondence of the trigeminal nerve and the right temple. At the time of reporting, the event was ongoing.

PPD (PPD) concerned a PPD year old PPD patient. The patient's past and current medical history included PPD Concomitant medication included PPD The patient received COVID-19 VACCINE ASTRAZENECA on PPD . On PPD , 3 days after vaccination, the patient experienced neuralgia. On an unknown date, the patient experienced hypophagia. ear infection, PPD , headache, and feeling cold. At the time of reporting, the event of neuralgia was ongoing. At the time of reporting, the event of hypophagia, ear infection, PPD , headache and feeling cold was improving. The patient was vaccinated on PPD 4.30 pm, PPD 4 am. PPD started feeling cold and shivery, body aches all over and headache. PPD took PPD and by PPD the symptoms had subsided but PPD had a dull headache. PPD felt good, then on PPD about 6 pm PPD had sharp electric pain in PPD right ear and right of PPD face. PPD saw the nurse on PPD thinking it was an ear infection and stated antibiotics, over the weekend the pain was excruciating and triggered by driving, drinking hot drinks eating hot food. PPD doctor assessed it as PPD likely to be caused by the vaccine. The symptoms are still present yet starting to subside with PPD and icing right side of the face. A dental X-ray ruled out any dental problems. This case could be confounded by the presence of concurrent ear infection.

PPD (PPD) concerned a PPD year old PPD patient. No relevant history was reported. Concomitant medication included PPD The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On PPD, 1 day after vaccination, the patient experienced PPD. On an unknown date, the patient experienced nerve pain. At the time of reporting, the event of nerve pain and PPD was improving. The patient described the events as: PPD

PPD (PPD): concerned a PPD year old PPD patient. No relevant history was reported. Concomitant medication included PPD The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On PPD, 1 day after vaccination, the patient experienced nerve pain and jaw pain On PPD, the patient experienced PPD. On an unknown date, the patient experienced PPD. At the time of reporting, the event of nerve pain, PPD and jaw pain was improving. Jaw ache started day after vaccine, then became worse and painful in jaws/cheeks/face 3 days after vaccine. Doctor discussed PPD and prescribed PPD

The 8 cases described events of Trigeminal neuralgia (5), Facial neuralgia (2), and Trigeminal nerve disorder (1), occurring 0-3 days after vaccination. In these 8 cases, outcome was ongoing in 2, recovered or recovering in 6. One case was possibly confounded by concurrent ear infection.

Herpes history

Four cases reported a previous or current history of herpes infection (PPD). This history included facial herpes, shingles, post herpetic neuralgia, and herpes on lip. In these cases the relevant events were all reported as Facial neuralgia, and occurred the same day as vaccination in 2 reports, after 1 day in 1 report, and 2 days in the remaining report:

PPD (**Facial neuralgia**) concerned a PPD year old PPD patient. No medical history or concomitant medications were reported, but the patient reported to have concurrent facial herpes. The patient received COVID-19 VACCINE ASTRAZENECA on PPD. On PPD, 1 day after vaccination, the patient experienced facial pain. At the time of reporting, the event of facial pain was ongoing. The description was given as: painful facial neuralgia, across PPD side of face - vaccine taken in right arm.

PPD (**Facial neuralgia**) concerned a PPD patient of unknown age. The patient's past and current medical history included PPD

PPD , and fever. No concomitant medications were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD . On PPD , 1 day after vaccination, the patient experienced mouth dry, fever, and headache. On PPD , 2 days after vaccination, the patient experienced neuralgia facial. On an unknown date, the patient experienced neuralgia. The patient recovered from the events of mouth dry, fever and headache after 1 day. At the time of reporting, the event of neuralgia facial was ongoing. At the time of reporting, the event of dry throat, neuralgia and fever was improving.

PPD (**Facial neuralgia**) concerned a PPD year old PPD patient. The patient's past and current medical history included PPD , and shingles (dates not reported). No concomitant medications were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD . The same day, the patient experienced facial neuralgia. On an unknown date, the patient experienced shingles. At the time of reporting, the event of neuralgia facial was ongoing. At the time of reporting, the event of shingles was improving.

PPD (**Facial neuralgia**) concerned a PPD year old PPD patient. No medical history or concomitant medications were reported. The patient received COVID-19 VACCINE ASTRAZENECA on PPD and on PPD . On PPD , same day as 2nd vaccination, the patient experienced facial neuralgia and herpes on lip. The patient recovered from the event of facial neuralgia after 1 day, and recovered from herpes on lip after 3 weeks.

Although concurrent/past herpes infection could be involved in these events, based on the small number of reports, it is not possible to definitively conclude this. The reported events were facial neuralgia, and trigeminal neuralgia was not diagnosed by a specialist.

Medically confirmed cases

Of the 171 cases, containing 187 events assessed as true trigeminal neuralgia, 26 events in 25 cases were medically confirmed, of which 14 were serious events:

Table 36 Seriousness for Medically Confirmed Events of Trigeminal Neuralgia

Preferred Term	Serious	Non Serious	Total
Trigeminal neuralgia	9	6	15
Facial neuralgia	2	4	6
Trigeminal nerve disorder	1	2	3
Trigeminal palsy	1	0	1
Trigeminal nerve paresis	1	0	1
Grand Total	**14**	**12**	**26**

Of the 25 medically confirmed cases, on review, none were diagnosed by specialist neurologist or dentist. In the 15 events of PT Trigeminal neuralgia, it was generally the HCP impression that there may have been trigeminal neuralgia but with no definitive diagnosis.

Observed Versus Expected Analysis

The observed events versus expected events analysis for trigeminal neuralgia events is presented in Table 37. As can be seen, for all categories presented, the observed numbers of events is significantly less than expected.

Table 37 Observed Versus Expected Analysis for Trigeminal Neuralgia Events

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Trigeminal Neuralgia All RW 42 days	42	4.3	110580529	169	546.78	0.31 (0.26 - 0.36)	Observed significantly < expected
Trigeminal Neuralgia All RW 42 days including cases with unknown TTO	42	4.3	110580529	227	546.78	0.42 (0.36 - 0.47)	Observed significantly < expected
Trigeminal Neuralgia Male RW 42 days UK	42	3.4	22245775	22	86.98	0.25 (0.16 - 0.38)	Observed significantly < expected
Trigeminal Neuralgia Female RW 42 days UK	42	5.9	23464773	81	159.2	0.51 (0.4 - 0.63)	Observed significantly < expected
Trigeminal Neuralgia Male RW 42 days including cases with unknown TTO UK	42	3.4	22245775	30	86.98	0.34 (0.23 - 0.49)	Observed significantly < expected

Table 37 Observed Versus Expected Analysis for Trigeminal Neuralgia Events

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Trigeminal Neuralgia Female RW 42 days including cases with unknown TTO UK	42	5.9	23464773	112	159.2	0.7 (0.58 - 0.85)	Observed significantly < expected

AEs Adverse Events, RW Risk Window, TTO Time To Onset, UK United Kingdom.

Literature review

A literature search was conducted to review the occurrence of terms relating to trigeminal neuralgia in association with COVID-19 ASTRAZENECA VACCINE, but retrieved no relevant articles.

eRMR data

Table 38 presents data from EudraVigilance Data Analysis System (EVDAS) for a number of different COVID-19 vaccines.

For COVID-19 Vaccine AstraZeneca, Reporting Odds Ratio (RoR) value from EVDAS was above 1 for the PTs Facial Neuralgia, Numb chin syndrome, Trigeminal neuralgia, and Trigeminal neuritis.

Table 38 eRMR data

Event Term	EVDAS RoR (date)					
	COVID-19 Vaccine AstraZeneca		COVID-19 mRNA VACCINE (NUCLEOSIDE-MODIFIED)	COVID-19 mRNA VACCINE MODERNA (CX-024414)	COVID-19 VACCINE JANSSEN (AD26.COV2.S)	COVID-19 VACCINE
	RoR	#Cases				
Facial neuralgia	3.58	53	-	1.12	0.24	4.99
Numb chin syndrome	1.18	4	-	11.70	-	-

Table 38 eRMR data

Event Term	EVDAS RoR (date)					
	COVID-19 Vaccine AstraZeneca		COVID-19 mRNA VACCINE (NUCLEOSIDE-MODIFIED)	COVID-19 mRNA VACCINE MODERNA (CX-024414)	COVID-19 VACCINE JANSSEN (AD26.COV2.S)	COVID-19 VACCINE
	RoR	#Cases				
Trigeminal nerve disorder	0.89	11	-	1.11	0.43	-
Trigeminal nerve paresis	0.15	1	-	0.80	-	-
Trigeminal neuralgia	1.69	115	-	1.36	-	0.30
Trigeminal neuritis	1.10	3	-	2.91	-	-
Trigeminal palsy	0.49	2	-	-	-	-

COVID-19 Coronavirus Disease 2019, eRMR electronic Reaction Monitoring Report, EVDAS EudraVigilance Data Analysis System, RoR Reporting Odds Ratio,

Conclusion

Where data were available most cases (69%) occurred with an onset 3 days or less after vaccination, with 51.9% occurring at 1 day or less. This time to onset may appear to show a plausible pattern that might indicate relatedness to vaccination, however the majority of reports were either of limited information or confounded by other factors. Eight cases (also with time to onset 0-3 days after vaccination) were considered on review to have no reasonable alternative causal factors noted. Only 1 of these 8 cases was medically confirmed. The 8 cases described events of Trigeminal neuralgia (5), Facial neuralgia (2), and Trigeminal nerve disorder (1), occurring 0-3 days after vaccination. In these 8 cases, outcome was ongoing in 2, recovered or recovering in 6. One case was confounded by concurrent ear infection.

Although concurrent/past herpes infection could be involved in some events, based on the small number of reports (4) involving herpes virus infection, it is not possible to definitively conclude this. Only 26 events were medically confirmed, of which, 14 were serious. Based on the small number of medically confirmed cases relating to trigeminal neuralgia, and the few cases (8) with no reasonable alternative causal factors noted (of which 1 was medically confirmed) it is not possible at this stage to confirm a causal relationship between COVID-19 VACCINE ASTRAZENECA and trigeminal neuralgia.

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. Trigeminal neuralgia 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 New information on Vaccine-associated enhanced disease (VAED)/ Vaccine-associated enhanced respiratory disease (VAERD) during the reporting period

Cumulatively, there have been 882 case reports of potential Vaccine-associated enhanced disease (VAED)/ (Vaccine-associated enhanced respiratory disease)VAERD including 969 events. During the period covered by this report 969 events from 882 cases were retrieved under this AESI concept, which include Pneumonia (431), Coagulopathy (222), COVID-19 pneumonia (90), Respiratory failure (77), Multiple organ dysfunction syndrome (44), Pneumonitis (44), Acute respiratory failure (21), Pulmonary Haemorrhage (15), Cytokine storm (7), Post-acute COVID-19 syndrome (7), Organ failure (4), Cytokine release syndrome (2), Vaccine associated enhanced disease (2), Acute lung injury (1), Cytokine increased (1) and Mechanical ventilation (1).

Of these 882 cases, 373 (339 serious and 34 non serious) were medically confirmed and 23 were reported after the second dose of COVID-19 Vaccine AstraZeneca. There were 243 case reports from elderly vaccinees and 348 from adult vaccinees; age was unknown for 291 vaccinees. In 162 of the 882 cases, the outcome of potential VAED/VAERD events was fatal.

There were 107 potential VAED/VAERD cases that tested positive for COVID-19 post-vaccination (range 1-67 days post-vaccination; unknown for 31 cases). Of these 107 cases, 96 were reported after the first dose and 11 after the second dose. Of the 96 cases after the first dose, and the outcome was fatal in 33 cases (18 elderly and 13 adult, vaccinees, 2 with unknown age). The causes of death in all of these 33 fatal cases after the first dose was COVID-19 pneumonia (19), COVID-19 (18), Haemorrhage (16), Blood ketone body present (15), Brain oedema (15), Coagulopathy (15), Immune system disorder (15), Immune-mediated adverse reaction (15) ,Skin discolouration (15), Brain stem haemorrhage (15), COVID-19 (14), COVID-19 pneumonia (9), Cardiac arrest (7), Ventricle rupture (5), Pneumonia (4), Pneumonitis (4), Respiratory failure (3), Asthenia (2), Cardiovascular insufficiency (2), Cerebrovascular accident (2), Condition aggravated (2), Pneumonia (2), Pyrexia (2), Thrombosis (2), Cerebral artery occlusion (2),, Anal incontinence (1), Arteriosclerosis coronary artery (1), Body temperature increased (1), Cardiac failure (1),, Chills (1), Coronavirus test positive (1),, Death (1), Dyspnoea (1),, Hemiparesis (1),, Nasopharyngitis (1), SARS-CoV-2 test positive (1), Seizure (1),, Septic shock (1),, Supine position (1), Thrombotic stroke (1), Acute respiratory distress syndrome (ARDS) (1), Aortic thrombosis (1), Decreased appetite (1), Ischaemic cardiomyopathy (1), Ischaemic stroke (1), Multiple

organ dysfunction syndrome (1), Pneumonia viral (1), SARS-CoV-2 test positive (1), Sepsis (1), Urinary incontinence (1).

Of the 11 cases after the second dose, the outcome was fatal in 3 cases 2 PPD patient (PPD and PPD year) and 1 adult PPD patient (PPD year) both died of COVID-19 pneumonia (3), Multiple organ dysfunction syndrome (1), ARDS (1), and cough (1) (limited information was provided concerning all these reports).

Information in these case reports was limited and no other laboratory parameters (including antibody titers, increased viral load, and inflammatory markers) were available for further assessment.

Based on further review and taking into account the timing of COVID-19 testing in relation to vaccination and limited information on laboratory parameters required for the assessment of potential VAED/VAERD, these 775 cases were not suggestive of confirmed VAED or VAERD and hence not included in Appendix 8.

Conclusion

From the data identified during the reporting period no causal relationship between VAED/VAERD and COVID-19 VACCINE ASTRAZENECA could be established. Notably, 107 of the 882 cases of potential VAED/VAERD received during the reporting period occurred 96 cases after the first dose of COVID-19 VACCINE ASTRAZENECA (1-67 days with 29 cases unknown time post-vaccination) and 11 cases occurred after the second dose (1-67 days with 2 unknown time post-vaccination).

36 of these 107 cases of potential had a fatal outcome. The vaccinee's comorbidities, concomitant medications, and storage and transport conditions of the vaccine are unknown.

Vaccine-associated enhanced disease is included as an Important Potential Risk in the core RMP and VAERD is an Important Potential Risk in the EU RMP. These topics 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 39 below are kept under close surveillance by AstraZeneca.

Table 39 Risks presented in Core RMP (Version 3; 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

A cumulative search of the AstraZeneca safety database was undertaken for AE reports under the HLT of "Thrombocytopenias" and SMQ of "Hematopoietic Thrombocytopenia-Narrow" co-reported with events identified from the SMQ of "Embolic and thrombotic events" in association with the use of COVID-19 VACCINE ASTRAZENECA. This covered the period up to 28 June 2021. Both open and closed cases were included in the search. The same search criteria was also used to retrieve case reports of Thrombosis with Thrombocytopenia Syndrome (TTS) following second dose of COVID-19 VACCINE ASTRAZENECA.

The search resulted in a total of 1375 individual open and closed cases (cumulative up to 28 June 2021), 1372 were serious and 3 were non-serious; 1041 case reports were medically confirmed and 334 were consumer reports. There were 67 cases with thrombosis in combination with TCP after second dose.

Of these 1375 case reports, 749 (54%) reports were reported in females, 588 (43%) reports in males, and in 38 (3%) cases the gender was not reported.

Forty-nine percent (675/49%) originated from UK and the other cases (>10) were from the following countries: Germany (166), Australia (125), Italy (75), Spain (52), France (38), Netherlands (36), Brazil (25), Belgium (24), Canada (23), Sweden (16), Norway (14), Austria (13), and Finland (11). The cumulative dose distribution in UK was 45892305 (11.7%) out to total worldwide 390841575 dose distribution.

Thirty-six percent (490) of the cases were reported for vaccinees aged 18-49 years; 19 % (265) in vaccinees aged 50-59 years, 21 % (289) in vaccinees aged 60-69 years, 12 % (159) in vaccinees aged 70-79 years, 4 % (60) in vaccinees aged ≥ 80 years, and in 8 % (112) vaccinees age was unknown. The median age was 55 years (for all cases; range 18 to 95 years).

Eighteen percent (245/1375) cases reported fatal outcome when compared to 19% (210 out of 1095), 22 % (150 fatal reports out of 679) and 27% (49 out of 184) in the May, April, and March MSSRs respectively; Fatality/survival rate cumulatively up to 28 June 2021 is presented in Table 49 and Figure 2. Case level outcome in remaining cases were not recovered (513), recovered (138), recovered with sequelae (23), recovering (286), and unknown (170).

Time to onset for TTS event was available in 1181 (86%) case reports and ranged from 1 day to 133 days; median TTO was 12 days. In 68% (800 out of 1181 reports) of the case reports, the TTS events occurred within 14 days after vaccination; 86 % (1012 out of 1181) and 96 % (1137 out of 1181) of the case reports were reported within 21 days and 42 after vaccination respectively.

Of the 1375 case reports reviewed, the reported venous thrombotic sites included (CVST-HLT of Cerebrovascular venous and sinus thrombosis) in 392 cases. Eighty-four case reports (6%) had the co-reported events from HLT of Coagulopathies (including 50 cases with disseminated intravascular coagulation) and 571 case reports (41.5 %) had co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)-Narrow. Most common (≥10) bleeding events included Cerebral haemorrhage (151), Haemorrhage (64), Subarachnoid haemrrhage (49), Haemorrhage intracranial (44), Contusion (36), Petechiae (22), Haemoptysis (20), Thrombotic thrombocytopenic purpura (17), Cerebral haematoma (16), Haemorrhagic stroke (13), Haematoma (11), and Haematuria (10).

Thrombosis in combination with thrombocytopenia case classification in alignment with MHRA case definitions

Based on the recommendation from PRAC Rapporteur (Preliminary - Assessment Report for the 3rd monthly summary safety update - Post-Opinion Measure 027.2), all 1375 case reports were reviewed as per the MHRA case definition in Figure 1.

Figure 1 MHRA Case Classification 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			

MHRA Medicines and Healthcare Products Regulatory Agency, PF-4 Platelet Factor-4.

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 report 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 950 (69%) of 1375 case reports; platelet count was $<150x10^9$/L in 916 of the 950 reports and in 34 case reports platelet count was $>150x10^9$/L. Among these 916 vaccinees with reported platelet count $<150x10^9$/L, 450 (49.1%) had a platelet count of $<50x10^9$/L. In remaining 425 (31%) of the 1375 case reports information on platelet count was not available.

In 6 of the 1375 case reports there was no venous/arterial thrombosis reported. PF-4 antibodies were positive in 299 (21.7%) reports, negative in 297 (21.6 %) reports, unknown or pending in 779 (56.7%) case reports.

D-dimer levels were reported in 622 (45.2 %) of the 1375 case reports, however, in many reports the units were not specified. In 158 (11.5%) D-dimer levels were < 4000 ng/mL and in 464 (33.7%) case reports D-dimer levels were > 4000 ng/mL. In 753 (54.8 %) case reports D-dimer levels were not provided/reported.

Of the 1375 case reports reviewed, the reported venous thrombotic sites included (CVST-HLT of Cerebrovascular venous and sinus thrombosis) in 392 cases, 293 case reports which met the classification of confirmed, probable or possible case, confirmed cases were 69 (24%).

Of the 1375 case reports reviewed, based on the above case classification criteria, the total number of confirmed cases were 174 (13%), probable cases were 269 (20%), possible cases were 466 (34%), unlikely 4 (0.3%) and criteria not met were 462 (34%). Out of all cases (909) which met the criteria, the confirmed cases (174) comprised 19% of the total cases. In all cases (909) where the diagnostic criteria was met, 374 (41%) cases had confounding factors. Many of the cases had more than one confounding factor. The confounding factors associated were: Autoimmune disease (93) {ITP (47), autoimmune thyroiditis (5), psoriasis (4), antiphospholipid syndrome (5), Crohn's disease (4), myasthenia gravis (3), Inflammatory bowel disease (3), ulcerative colitis (3), ankylosing spondylitis (2), rheumatoid arthritis (2), Guillain-barre syndrome (2), sarcoidosis (2), systemic lupus erythematous (2), autoimmune hepatitis (2), vasculitis (1), multiple sclerosis (1), Hemolytic anemia (1), Polymyalgia rheumatica (1), Thalassemia minor (1) and Connective tissue disorder (1)}; Malignancy (61) {breast cancer (12), prostate cancer (5), malignant melanoma (3), brain cancer (2), thyroid cancer (2), non-Hodgkin's lymphoma (2), polycythemia vera (2), bladder cancer (1), gastrointestinal cancer (1), pituitary tumor (1), lung cancer (2), metastatic cancer (1), tonsil cancer (1), ovarian cancer (1), pancreatic cancer (1), testicular cancer (1), uterine cancer (2), vulvar cancer (1), cervix carcinoma (1), renal cell carcinoma (1), chronic lymphocytic leukemia (1), glioblastoma (1), gliomas (1), leukemia (1), lymphoma (1), lymphoproliferative

disease (1), metastatic neoplasm (1), myelodysplastic neoplasm (2), neoplasm (3), sarcoma (1)}; Past history of heparin (88) information on the dates of heparin administration was not available, Obesity (51), Past and current history of Contraceptive (38), Past history of thrombosis (23), HIT (12), Past history of frequent abortion (4), HIV infection (2), Chronic Hepatitis B (1), Liver disease (2), COVID-19 illness (2), Cardiomyopathy resulting from Fredrich's ataxia (1), Chronic kidney disease (1), Chronic glomerulonephritis (1), Dress syndrome (1), Immobility (1), Liver transplant (1), Past history of stroke (1), Peripheral vascular disease (1), Polycystic ovary syndrome (1), Protein C deficiency (1), Sickle cell disease (1), TCP chronic (1).Concomitant medications; Venaflaxine (2), and Citalopram and Clopidogrel combination (1).

In out of 174 confirmed reports, there were 84 (48%) cases with confounding factors. The confounding factor associated were; Past history of heparin (19), cancer (11) {Neoplasm (1), Prostate cancer (1), Vulvar cancer (1), Metastatic cancer (1), pancreatic cancer (1) Cancer uterus (2), Myelodysplastic syndrome (1), Hodgkin's disease (1), Non-Hodgkin's disease (1), breast cancer(1), malignant melanoma (1)}, Obesity (18), Contraceptives (9), ITP (13), Autoimmune disease (5) {Sarcoidosis (1), Guillain-Barre syndrome (1), Myasthenia gravis (1), Ankylosing Spondylitis (1), autoimmune thyroiditis (1), antiphospholipid syndrome (1). Crohn's disease (1)}, HIT (5), Past history of thrombosis (5), Chronic kidney disease (1), Peripheral vascular disease (1), Ulcerative colitis (1). The dates of heparin administered was not reported in all cases.

Demographics and Clinical characteristics of cases based on the above criteria are mentioned in Table 40 and Table 41 respectively.

Table 40 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed reports (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Median age in years (range)	55 (18-95)	47 (20-78)	55 (18-92)	56 (18-95)	65 (60-72)	56 (18-95)
Sex						
Female n (%)	749 (54.5)	94 (6.8)	150 (10.9)	266 (19.3)	1 (0.1)	238 (17.3)
Male n (%)	588 (42.8)	79 (5.7)	117 (8.5)	197 (14.3)	3 (0.2)	192 (14)
Unknown n (%)	38 (2.8)	1 (0.1)	2 (0.1)	3 (0.2)	0 (0)	32 (2.3)
Region n (%)						
EEA						
Germany	166 (12.1)	5 (0.4)	16 (1.2)	47 (3.4)	0 (0)	98 (7.1)
Italy	75 (5.5)	0 (0)	11 (0.8)	13 (0.9)	0 (0)	51 (3.7)
Spain	52 (3.8)	6 (0.4)	8 (0.6)	16 (1.2)	0 (0)	22 (1.6)
France	38 (2.8)	0 (0)	2 (0.1)	8 (0.6)	0 (0)	28 (2)
Netherlands	36 (2.6)	2 (0.1)	13 (0.9)	12 (0.9)	0 (0)	9 (0.7)
Belgium	24 (1.7)	4 (0.3)	1 (0.1)	5 (0.4)	0 (0)	14 (1)
Sweden	16 (1.2)	0 (0)	0 (0)	2 (0.1)	0 (0)	14 (1)
Norway	14 (1)	3 (0.2)	3 (0.2)	3 (0.2)	0 (0)	5 (0.4)
Austria	13 (0.9)	1 (0.1)	4 (0.3)	4 (0.3)	0 (0)	4 (0.3)
Finland	11 (0.8)	0 (0)	0 (0)	1 (0.1)	0 (0)	10 (0.7)
Greece	9 (0.7)	0 (0)	2 (0.1)	5 (0.4)	0 (0)	2 (0.1)
Poland	8 (0.6)	0 (0)	0 (0)	5 (0.4)	0 (0)	3 (0.2)
Ireland	6 (0.4)	2 (0.1)	0 (0)	4 (0.3)	0 (0)	0 (0)
Portugal	4 (0.3)	0 (0)	1 (0.1)	2 (0.1)	0 (0)	1 (0.1)
Denmark	4 (0.3)	1 (0.1)	0 (0)	2 (0.1)	0 (0)	1 (0.1)

Table 40 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed reports (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Hungary	4 (0.3)	0 (0)	0 (0)	2 (0.1)	0 (0)	2 (0.1)
Malta	3 (0.2)	0 (0)	0 (0)	1 (0.1)	0 (0)	2 (0.1)
Bulgaria	3 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.2)
Latvia	2 (0.1)	0 (0)	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Czech Republic	2 (0.1)	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)
Slovenia	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)
Estonia	2 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Luxembourg	2 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Lithuania	2 (0.1)	0 (0)	0 (0)	2 (0.1)	0 (0)	0 (0)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)
[redacted]	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
UK						
United Kingdom	675 (49.1)	140 (10.2)	189 (13.7)	249 (18.1)	4 (0.3)	93 (6.8)
Rest of the World						
Australia	125 (9.1)	0 (0)	7 (0.5)	64 (4.7)	0 (0)	54 (3.9)
Brazil	25 (1.8)	4 (0.3)	8 (0.6)	3 (0.2)	0 (0)	10 (0.7)
Canada	23 (1.7)	4 (0.3)	0 (0)	0 (0)	0 (0)	19 (1.4)
India	7 (0.5)	0 (0)	0 (0)	5 (0.4)	0 (0)	2 (0.1)
Sri Lanka	6 (0.4)	0 (0)	0 (0)	6 (0.4)	0 (0)	0 (0)
Korea, Republic of	3 (0.2)	1 (0.1)	0 (0)	0 (0)	0 (0)	2 (0.1)

Table 40 Demographics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed reports (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Mexico	2 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)	(0)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
[redacted]	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Seriousness						
Serious	1372	174	269	464	4	461
Non-serious	3	0	0	2	0	1
Medical confirmation						
Medically confirmed	1041	151	234	350	3	303
Consumer reports	334	23	35	116	1	159

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
AZD1222 dose						
Dose 1	1308	172	250	430	4	452
Dose 2	67	2	19	36	0	10

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Median Time to onset in days: AZD1222 Dose 1	12	12	13	12	26	11
Median Time to onset in days: AZD1222 Dose 2	10	13	8	13	NA	4
Thrombosis site						
Embolic and thrombotic events, arterial (SMQ)	77	8	13	17	0	39
Embolic and thrombotic events, venous (SMQ)	701	88	141	255	1	216
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)	266	15	41	84	1	125
Multiple site of thrombosis	327	63	74	110	2	78
Embolic and thrombotic events, venous (SMQ)						

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Pulmonary embolism	428	55	114	137	1	121
Cerebral venous sinus thrombosis	290	55	56	105	1	73
Deep vein thrombosis	203	26	38	78	1	60
Portal vein thrombosis	98	21	18	31		28
Cerebral venous thrombosis	77	11	11	31	1	23
Superior sagittal sinus thrombosis	41	12	7	18		4
Mesenteric vein thrombosis	38	7	8	9		14
Jugular vein thrombosis	32	7	4	8		13
Splenic vein thrombosis	30	3	9	8		10
Venous thrombosis	30	4	7	9		10
Hepatic vein thrombosis	27	5	7	8		7
Visceral venous thrombosis	20	7	5	6		2
Pelvic venous thrombosis	16	1	4	7		4

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Thrombophlebitis	13	1	2	4		6
Thrombophlebitis superficial	13	2	3	3		5
Renal vein thrombosis	11	1	6	2		2
Transverse sinus thrombosis	10	3	2	3		2
Pulmonary thrombosis	9	3		2		4
Venous thrombosis limb	7		1	1		5
Portosplenomesenteric venous thrombosis	7		1			6
Pulmonary infarction	6	1	2	1		2
Ophthalmic vein thrombosis	4		1	3		
Ovarian vein thrombosis	4		1	2		1
Vena cava thrombosis	3		1	1		1
Embolism venous	3	1	1			1
Portal vein occlusion	3	1		2		

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Cavernous sinus thrombosis	3	1		1		1
Retinal vein occlusion	2			1		1
Jugular vein occlusion	2	2				
Splenic vein occlusion	1			1		
Portal vein embolism	1					1
Vena cava filter insertion	1					1
Portal vein cavernous transformation	1			1		
Venoocclusive liver disease	1			1		
Hepatic vein occlusion	1	1				
Retinal vein thrombosis	1			1		
Pulmonary venous thrombosis	1					1
Renal vein embolism	1	1				

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Budd-Chiari syndrome	1			1		
Embolic and thrombotic events, arterial (SMQ)						
Ischaemic stroke	34	4	5	7		18
Aortic thrombosis	25	5	4	10	1	5
Peripheral artery thrombosis	25	7	4	10		4
Arterial thrombosis	19	3	7	4		5
Carotid artery thrombosis	18	5	3	7		3
Thrombotic thrombocytopenic purpura	17	2	2	3		10
Myocardial infarction	17	3	3	7	1	3
Acute myocardial infarction	15	2	7	2		4
Transient ischaemic attack	11		1	1		9
Aortic embolus	11	1	4	4	1	1
Cerebral artery thrombosis	10	1	2	4		3

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Coronary artery thrombosis	8	2	3	3		
Ischaemic cerebral infarction	6	2	1	2		1
Peripheral embolism	5	1		2		2
Peripheral artery occlusion	5	1		4		
Pulmonary artery thrombosis	5	1	1	1		2
Splenic artery thrombosis	5		1	2		2
Cerebral artery occlusion	4	1	1	1		1
Hepatic artery thrombosis	3		2	1		
Embolism arterial	3		2			1
Carotid artery occlusion	3	1	2			
Mesenteric artery thrombosis	3		1			2
Peripheral arterial occlusive disease	3		1	2		
Pulmonary artery occlusion	2			2		

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Renal artery thrombosis	2			1		1
Thromboembolectomy	1		1			
Truncus coeliacus thrombosis	1					1
Cerebral artery embolism	1			1		
Arterial occlusive disease	1			1		
Internal capsule infarction	1			1		
Iliac artery occlusion	1				1	
Thrombotic microangiopathy	1					1
Renal artery occlusion	1				1	
Femoral artery embolism	1		1			
Coronary artery bypass	1					1
Lacunar infarction	1					1
Renal embolism	1		1			

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)						
Thrombosis	254	24	44	72		114
Embolism	62	6	14	28		14
Hemiparesis	53	13	16	19		5
Disseminated intravascular coagulation	50	7	18	7	1	17
Cerebrovascular accident	46	4	4	24		14
Cerebral infarction	40	6	6	15		13
Cerebral thrombosis	35	4	8	12		11
Heparin-induced thrombocytopenia	25	6	4	6	1	8
Hemiplegia	14	1	1	4		8
Haemorrhagic stroke	13	3	1	5		4
Splenic infarction	11	1	3	4		3
Haemorrhagic transformation stroke	7	1	1	4		1

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Renal infarct	6	1	2	1	1	1
Haemorrhagic cerebral infarction	5		2	3		
Infarction	5	2		3		
Intracardiac thrombus	5		2	2		1
Thrombosis mesenteric vessel	5	2	2	1		
Haemorrhagic infarction	4		1	2		1
Haemorrhagic adrenal infarction	4	1	1	1		1
Cardiac ventricular thrombosis	4	2	1	1		
Cerebral ischaemia	4	1	1	1		1
Intestinal infarction	4		1	3		
Splenic thrombosis	3	1		1		1
Thrombotic stroke	3		1	1		1
Atrial thrombosis	3	1		2		
Hepatic vascular thrombosis	3					3

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Hepatic infarction	3	1	1			1
Antiphospholipid syndrome	3		1	1		1
Monoparesis	2		2			
Cerebellar infarction	2	1		1		
Renal vascular thrombosis	2			1		1
Adrenal thrombosis	2		2			
Embolic stroke	1		1			
Thrombosis in device	1				1	
Haemorrhoids thrombosed	1					1
Vascular graft thrombosis	1			1		
Quadriplegia	1		1			
Vascular stent thrombosis	1			1		
Pancreatic infarction	1					1
Thalamic infarction	1			1		
Monoplegia	1			1		

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Brain stem infarction	1			1		
Platelet count						
<150 x 10^9/L n (%)	916 (66.6)	174 (12.7)	269 (19.6)	466 (33.9)	3 (0.2)	4 (0.3)
<50 x 10^9/L n (%)	450 (49.1)	105 (60.3)	138 (51.3)	204 (43.8)	2 (66.7)	1 (25)
50-100 x 10^9/L n (%)	244 (26.6)	48 (27.6)	72 (26.8)	122 (26.2)	0 (0)	2 (50)
100-150 x 10^9/L n (%)	166 (18.1)	16 (9.2)	48 (17.8)	100 (21.5)	1 (33.3)	1 (25)
Reported as < 150 x 10^9/L, however value not provided n (%)	56 (6.1)	5 (2.9)	11 (4.1)	40 (8.6)	(0)	(0)
>150 x 10^9/L or 'normal' n (%)	34 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	34 (2.5)
Unknown n (%)	425 (30.9)	(0)	(0)	(0)	1 (0.1)	424 (30.8)
Coagulopathy-n (%)	84 (6.1%)	12 (0.9%)	25 (1.8%)	16 (1.2%)	1 (0.1%)	30 (2.2%)

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)-Narrow* (≥10 events)	479 (34.8)	88 (6.4)	110 (8)	163 (11.9)	2 (0.1)	116 (8.4)
Cerebral haemorrhage	151	26	26	58		41
Haemorrhage	64	18	22	19		5
Disseminated intravascular coagulation	50	7	18	7	1	17
Subarachnoid haemorrhage	49	15	11	20		3
Haemorrhage intracranial	44	4	13	21		6
Contusion	36	7	7	16	1	5
Petechiae	22	4	5	12		1
Haemoptysis	20	4	7	4		5
Thrombotic thrombocytopenic purpura	17	2	2	3		10
Cerebral haematoma	16	2	7	5		2

Table 41 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	All case reports (n=1375)	Confirmed report (n=174)	Probable reports (n=269)	Possible reports (n=466)	Unlikely (n=4)	Criteria not met (n=462)
Haemorrhagic stroke	13	3	1	5		4
Haematoma	11	1	3	5		2
Haematuria	10	5	1	4		

n Number, SMQ Standardised MedDRA Query.

Reporting Rate and Observed versus Expected Analysis for TTS

Reporting rate for thrombosis in combination with thrombocytopenia and CVST and TCP across age groups based on the data from UK are provided in Table 42 and Table 43 respectively. Vaccine administration data for age groups "18-39" and "40-49" were extrapolated based on the distribution for all COVID-19 vaccines in EEA. Data from 4 top used Vaccines (Pfizer; AstraZeneca; Moderna; J&J) representing 98% of the EU/EEA Market (33.4M) by April 2021 in age groups 18-39; 40-49; 50-64; 64+ were used to calculate COVID-19 VACCINE ASTRAZENECA exposure in the UK. The proportion of doses in 18-39 and 40-49 groups for the period ending 28 June 2021 were calculated as 48% and 52% correspondingly from the 18-49 group administration data. Exposure in 18-49 years was 14.1 million and after extrapolation, exposure in 18-39 and 40-49 age group was 6.7 and 7.4 million respectively.

Table 42 Reporting rate for thrombosis in combination with thrombocytopenia (United Kingdom data)

Age Group	Total Exposed (in million)	All cases within Risk Window of 21 days	Reporting Rate for all cases (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)
18-39	6.7	95	14.2	2.1-3.2	11 to 12.1
40-49	7.4	122	16.5	3.4-6.3	10.2 to 13.1
50-64	18.3	155	8.5	7.3-14.9	-6.4 to 1.2
65+	13.2	95	7.2	23.4-44.4	-37.2 to -16.2
Age Unknown	0.2	30	150.0	-	N/A
Total	**45.8**	**497**	**10.9**	**5.6-10.7**	**0.2 to 5.3**

[a] background event rates per 1M PY per 21 days from Truven Market Scan-2019, aligned with the OHDSI TTS algorithm and Truven Market Scan-2019.

Table 43 Reporting rate for CVST and thrombocytopenia (UK data)

Age Group	Total Exposed (in million)	All cases within Risk Window of 21 days	Reporting Rate for all cases (per million)	Background Rate (per million)[a]	Rate relative to Background (per million)
18-39	6.7	49	7.3	0.1	7.2
40-49	7.4	51	6.9	0.1	6.8
50-64	18.3	54	3.0	0.2	2.8
65+	13.2	7	0.5	0.2	0.3
Age Unknown	0.2	7	35.0		N/A
Total	**45.8**	**168**	**3.7**	**0.1**	**3.6**

[a] background event rates per 1M PY per 21 days from Truven Market Scan-2019

CVST Cerebral Venous Sinus Thrombosis; UK United Kingdom.

Overall UK TTS reporting rate was 11/million (498 identified reports with time to onset ≤ 21 days; estimated exposure 45.8 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). 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 CVST+ TCP was higher across the age groups, when compared to the background rate.

Observed versus expected analyses for TTS (including CVST) and CVST with TCP are presented below. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned codelists and definitions for TTS. Algorithm 2 for TTS uses updated OHDSI-aligned codelists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded). Based on O/E analyses for TTS, the majority of reported events occurred in individuals aged 18-59 years regardless of sex.

Table 44 Observed versus Expected Analysis for TTS (Overall)

Adverse Events	Risk window[a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	
TTS Overall	14	9.77[b]	110580529	800	414.11	1.93 (1.8-2.07)	Observed significantly > expected
TTS Overall	21	9.77[b]	110580529	1012	621.17	1.63 (1.53-1.73)	Observed significantly > expected
TTS Overall	42	9.77[b]	110580529	1137	1242.34	0.92 (0.86-0.97)	Observed significantly < expected
TTS Overall	14	11.14[c]	110580529	800	472.18	1.69 (1.58-1.82)	Observed significantly > expected
TTS Overall	21	11.14[c]	110580529	1012	708.27	1.43 (1.34-1.52)	Observed significantly > expected
TTS Overall	42	11.14[c]	110580529	1137	1416.55	0.8 (0.76-0.85)	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

[b] Incidence Rate 9.77/100,000 PY from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm

[c] Incidence Rate 11.14/100,000 PY from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods

CI Confidence interval; CVST Cerebral Venous Sinus Thrombosis; OHDSI Observational Health Data Science and Informatics; TTS Thrombosis with thrombocytopenia syndrome.

Table 45 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window[a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - 18-49	14	4.53	23883226	317	41.47	7.64 (6.83-8.53)	Observed significantly > expected
TTS - 50-59	14	10.4	18157095	136	72.38	1.88 (1.58-2.22)	Observed significantly > expected
TTS - 60-69	14	19.19	22337254	153	164.31	0.93 (0.79-1.09)	Observed < expected
TTS - 70-79	14	38.93	12164855	62	181.53	0.34 (0.26-0.44)	Observed significantly < expected
TTS - over 80	14	59.54	3509828	20	80.1	0.25 (0.15-0.39)	Observed significantly < expected
TTS - 18-49	21	4.53	23883226	378	62.21	6.08 (5.48-6.72)	Observed significantly > expected
TTS - 50-59	21	10.4	18157095	182	108.57	1.68 (1.44-1.94)	Observed significantly > expected
TTS - 60-69	21	19.19	22337254	202	246.46	0.82 (0.71-0.94)	Observed significantly < expected

Table 45 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window[a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	
TTS - 70-79	21	38.93	12164855	86	272.29	0.32 (0.25-0.39)	Observed significantly < expected
TTS - over 80	21	59.54	3509828	24	120.15	0.2 (0.13-0.3)	Observed significantly < expected
TTS - 18-49	42	4.53	23883226	408	124.41	3.28 (2.97-3.61)	Observed significantly > expected
TTS - 50-59	42	10.4	18157095	207	217.14	0.95 (0.83-1.09)	Observed < expected
TTS - 60-69	42	19.19	22337254	229	492.92	0.46 (0.41-0.53)	Observed significantly < expected
TTS - 70-79	42	38.93	12164855	106	544.58	0.19 (0.16-0.24)	Observed significantly < expected
TTS - over 80	42	59.54	3509828	31	240.3	0.13 (0.09-0.18)	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 - 18-49	14	4.99	23883226	317	45.68	6.94 (6.2-7.75)	Observed significantly > expected

Table 45 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window[a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	
TTS - 50-59	14	12.6	18157095	136	87.69	1.55 (1.3-1.83)	Observed significantly > expected
TTS - 60-69	14	22.33	22337254	153	191.19	0.8 (0.68-0.94)	Observed significantly < expected
TTS - 70-79	14	44.66	12164855	62	208.24	0.3 (0.23-0.38)	Observed significantly < expected
TTS - over 80	14	58.18	3509828	20	78.27	0.26 (0.16-0.39)	Observed significantly < expected
TTS - 18-49	21	4.99	23883226	378	68.52	5.52 (4.97-6.1)	Observed significantly > expected
TTS - 50-59	21	12.6	18157095	182	131.54	1.38 (1.19-1.6)	Observed significantly > expected
TTS - 60-69	21	22.33	22337254	202	286.79	0.7 (0.61-0.81)	Observed significantly < expected
TTS - 70-79	21	44.66	12164855	86	312.37	0.28 (0.22-0.34)	Observed significantly < expected
TTS - over 80	21	58.18	3509828	24	117.41	0.2 (0.13-0.3)	Observed significantly < expected

Table 45 Observed versus Expected Analysis for TTS by age group (EU/UK)

Adverse Events	Risk window[a]	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	
TTS - 18-49	42	4.99	23883226	408	137.04	2.98 (2.7-3.28)	Observed significantly > expected
TTS - 50-59	42	12.6	18157095	207	263.08	0.79 (0.68-0.9)	Observed significantly < expected
TTS - 60-69	42	22.33	22337254	229	573.57	0.4 (0.35-0.45)	Observed significantly < expected
TTS - 70-79	42	44.66	12164855	106	624.73	0.17 (0.14-0.21)	Observed significantly < expected
TTS - over 80	42	58.18	3509828	31	234.82	0.13 (0.09-0.19)	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; CVST Cerebral venous sinus thrombosis; EU European Union; OHDSI Observational Health Data Science and Informatics; TTS Thrombosis with thrombocytopenia syndrome; UK United Kingdom

Table 46 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)	
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - Female UK	14	8.2	23464773	198	73.75	2.68 (2.32-3.09)	Observed significantly > expected

Table 46 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)	
TTS - Male UK	14	11.49	22245775	179	97.97	1.83 (1.57-2.12)	Observed significantly > expected
TTS - Female 18-49	14	4.53	7535741	99	13.08	7.57 (6.15-9.21)	Observed significantly > expected
TTS - Female 50-59	14	9.07	6160471	35	21.42	1.63 (1.14-2.27)	Observed significantly > expected
TTS - Female 60-69	14	12.88	4710221	28	23.25	1.2 (0.8-1.74)	Observed > expected
TTS - Female 70-79	14	31.05	3457691	15	41.15	0.36 (0.2-0.6)	Observed significantly < expected
TTS - Female over 80	14	40.77	1600649	8	25.01	0.32 (0.14-0.63)	Observed significantly < expected
TTS - Male 18-49	14	4.54	6635899	78	11.55	6.75 (5.34-8.43)	Observed significantly > expected
TTS - Male 50-59	14	11.87	6758081	44	30.75	1.43 (1.04-1.92)	Observed significantly > expected
TTS - Male 60-69	14	26.19	4784978	24	48.04	0.5 (0.32-0.74)	Observed significantly < expected

Table 46 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)	
TTS - Male 70-79	14	48.22	3116346	19	57.6	0.33 (0.2-0.52)	Observed significantly < expected
TTS - Male over 80	14	86.28	950471	7	31.43	0.22 (0.09-0.46)	Observed significantly < expected
TTS - Female UK	21	8.2	23464773	264	110.63	2.39 (2.11-2.69)	Observed significantly > expected
TTS - Male UK	21	11.49	22245775	231	146.96	1.57 (1.38-1.79)	Observed significantly > expected
TTS - Female 18-49	21	4.53	7535741	120	19.63	6.11 (5.07-7.31)	Observed significantly > expected
TTS - Female 50-59	21	9.07	6160471	53	32.13	1.65 (1.24-2.16)	Observed significantly > expected
TTS - Female 60-69	21	12.88	4710221	40	34.88	1.15 (0.82-1.56)	Observed > expected
TTS - Female 70-79	21	31.05	3457691	25	61.73	0.4 (0.26-0.6)	Observed significantly < expected
TTS - Female over 80	21	40.77	1600649	9	37.52	0.24 (0.11-0.46)	Observed significantly < expected

Table 46 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)	
TTS - Male 18-49	21	4.54	6635899	97	17.32	5.6 (4.54-6.83)	Observed significantly > expected
TTS - Male 50-59	21	11.87	6758081	59	46.12	1.28 (0.97-1.65)	Observed > expected
TTS - Male 60-69	21	26.19	4784978	34	72.05	0.47 (0.33-0.66)	Observed significantly < expected
TTS - Male 70-79	21	48.22	3116346	23	86.4	0.27 (0.17-0.4)	Observed significantly < expected
TTS - Male over 80	21	86.28	950471	7	47.15	0.15 (0.06-0.31)	Observed significantly < expected
TTS - Female UK	42	8.2	23464773	300	221.26	1.36 (1.21-1.52)	Observed significantly > expected
TTS - Male UK	42	11.49	22245775	273	293.92	0.93 (0.82-1.05)	Observed < expected
TTS - Female 18-49	42	4.53	7535741	131	39.25	3.34 (2.79-3.96)	Observed significantly > expected
TTS - Female 50-59	42	9.07	6160471	61	64.25	0.95 (0.73-1.22)	Observed < expected
TTS - Female 60-69	42	12.88	4710221	45	69.76	0.65 (0.47-0.86)	Observed significantly < expected

Table 46 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)	
TTS - Female 70-79	42	31.05	3457691	31	123.46	0.25 (0.17-0.36)	Observed significantly < expected
TTS - Female over 80	42	40.77	1600649	12	75.04	0.16 (0.08-0.28)	Observed significantly < expected
TTS - Male 18-49	42	4.54	6635899	104	34.64	3 (2.45-3.64)	Observed significantly > expected
TTS - Male 50-59	42	11.87	6758081	71	92.24	0.77 (0.6-0.97)	Observed significantly < expected
TTS - Male 60-69	42	26.19	4784978	44	144.11	0.31 (0.22-0.41)	Observed significantly < expected
TTS - Male 70-79	42	48.22	3116346	31	172.8	0.18 (0.12-0.25)	Observed significantly < expected
TTS - Male over 80	42	86.28	950471	10	94.3	0.11 (0.05-0.2)	Observed significantly < expected
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned code lists and washout periods							
TTS - Female UK	14	9.22	23464773	198	82.93	2.39 (2.07-2.74)	Observed significantly > expected

Table 46 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)	
TTS - Male UK	14	13.24	22245775	179	112.9	1.59 (1.36-1.84)	Observed significantly > expected
TTS - Female 18-49	14	4.64	7535741	99	13.4	7.39 (6-8.99)	Observed significantly > expected
TTS - Female 50-59	14	10.71	6160471	35	25.29	1.38 (0.96-1.92)	Observed > expected
TTS - Female 60-69	14	15.87	4710221	28	28.65	0.98 (0.65-1.41)	Observed < expected
TTS - Female 70-79	14	36.7	3457691	15	48.64	0.31 (0.17-0.51)	Observed significantly < expected
TTS - Female over 80	14	39.61	1600649	8	24.3	0.33 (0.14-0.65)	Observed significantly < expected
TTS - Male 18-49	14	5.36	6635899	78	13.63	5.72 (4.52-7.14)	Observed significantly > expected
TTS - Male 50-59	14	14.7	6758081	44	38.08	1.16 (0.84-1.55)	Observed > expected
TTS - Male 60-69	14	29.51	4784978	24	54.12	0.44 (0.28-0.66)	Observed significantly < expected
TTS - Male 70-79	14	54.04	3116346	19	64.55	0.29 (0.18-0.46)	Observed significantly < expected

Table 46 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)	
TTS - Male over 80	14	84.62	950471	7	30.83	0.23 (0.09-0.47)	Observed significantly < expected
TTS - Female UK	21	9.22	23464773	264	124.39	2.12 (1.87-2.39)	Observed significantly > expected
TTS - Male UK	21	13.24	22245775	231	169.35	1.36 (1.19-1.55)	Observed significantly > expected
TTS - Female 18-49	21	4.64	7535741	120	20.1	5.97 (4.95-7.14)	Observed significantly > expected
TTS - Female 50-59	21	10.71	6160471	53	37.94	1.4 (1.05-1.83)	Observed significantly > expected
TTS - Female 60-69	21	15.87	4710221	40	42.98	0.93 (0.66-1.27)	Observed < expected
TTS - Female 70-79	21	36.7	3457691	25	72.96	0.34 (0.22-0.51)	Observed significantly < expected
TTS - Female over 80	21	39.61	1600649	9	36.45	0.25 (0.11-0.47)	Observed significantly < expected
TTS - Male 18-49	21	5.36	6635899	97	20.45	4.74 (3.85-5.79)	Observed significantly > expected

Table 46 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)	
TTS - Male 50-59	21	14.7	6758081	59	57.12	1.03 (0.79-1.33)	Observed > expected
TTS - Male 60-69	21	29.51	4784978	34	81.19	0.42 (0.29-0.59)	Observed significantly < expected
TTS - Male 70-79	21	54.04	3116346	23	96.83	0.24 (0.15-0.36)	Observed significantly < expected
TTS - Male over 80	21	84.62	950471	7	46.24	0.15 (0.06-0.31)	Observed significantly < expected
TTS - Female UK	42	9.22	23464773	300	248.78	1.21 (1.07-1.35)	Observed significantly > expected
TTS - Male UK	42	13.24	22245775	273	338.69	0.81 (0.71-0.91)	Observed significantly < expected
TTS - Female 18-49	42	4.64	7535741	131	40.21	3.26 (2.72-3.87)	Observed significantly > expected
TTS - Female 50-59	42	10.71	6160471	61	75.87	0.8 (0.62-1.03)	Observed < expected
TTS - Female 60-69	42	15.87	4710221	45	85.96	0.52 (0.38-0.7)	Observed significantly < expected

Table 46 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)	
TTS - Female 70-79	42	36.7	3457691	31	145.92	0.21 (0.14-0.3)	Observed significantly < expected
TTS - Female over 80	42	39.61	1600649	12	72.91	0.16 (0.09-0.29)	Observed significantly < expected
TTS - Male 18-49	42	5.36	6635899	104	40.9	2.54 (2.08-3.08)	Observed significantly > expected
TTS - Male 50-59	42	14.7	6758081	71	114.24	0.62 (0.49-0.78)	Observed significantly < expected
TTS - Male 60-69	42	29.51	4784978	44	162.37	0.27 (0.2-0.36)	Observed significantly < expected
TTS - Male 70-79	42	54.04	3116346	31	193.66	0.16 (0.11-0.23)	Observed significantly < expected
TTS - Male over 80	42	84.62	950471	10	92.49	0.11 (0.05-0.2)	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; CVST Cerebral Venous Sinus Thrombosis; OHDSI Observational Health Data Science and Informatics; TTS Thrombosis with thrombocytopenia syndrome

Table 47 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)	
CVST-TCP - Overall	14	0.25	110580529	278	10.6	26.23 (23.23 - 29.5)	Observed significantly > expected
CVST-TCP - Overall	21	0.25	110580529	333	15.89	20.96 (18.77 - 23.33)	Observed significantly > expected
CVST-TCP - Overall	42	0.25	110580529	354	31.79	11.14 (10.01 - 12.36)	Observed significantly > expected
Observed versus Expected Analysis for CVST+TCP by age group (EU/UK)							
CVST-TCP - 18-49	14	0.17	23883226	168	1.56	107.69 (92.02 - 125.26)	Observed significantly > expected
CVST-TCP - 50-59	14	0.39	18157095	47	2.71	17.34 (12.74 - 23.06)	Observed significantly > expected
CVST-TCP - 60-69	14	0.33	22337254	49	2.83	17.31 (12.81 - 22.89)	Observed significantly > expected
CVST-TCP - 70-79	14	0.38	12164855	3	1.77	1.69 (0.35 - 4.95)	Observed > expected
CVST+TCP:80 +	14	0	3509828	2	0	Inf (Inf - Inf)	Observed significantly > expected

Table 47 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)	
CVST-TCP - 18-49	21	0.17	23883226	183	2.33	78.54 (67.57 - 90.78)	Observed significantly > expected
CVST-TCP - 50-59	21	0.39	18157095	56	4.07	13.76 (10.39 - 17.87)	Observed significantly > expected
CVST-TCP - 60-69	21	0.33	22337254	57	4.24	13.44 (10.18 - 17.42)	Observed significantly > expected
CVST-TCP - 70-79	21	0.38	12164855	4	2.66	1.5 (0.41 - 3.85)	Observed > expected
CVST+TCP:80 +	21	0	3509828	2	0	Inf (Inf - Inf)	Observed significantly > expected
CVST-TCP - 18-49	42	0.17	23883226	192	4.67	41.11 (35.5 - 47.36)	Observed significantly > expected
CVST-TCP - 50-59	42	0.39	18157095	60	8.14	7.37 (5.62 - 9.49)	Observed significantly > expected
CVST-TCP - 60-69	42	0.33	22337254	64	8.48	7.55 (5.81 - 9.64)	Observed significantly > expected
CVST-TCP - 70-79	42	0.38	12164855	5	5.32	0.94 (0.31 - 2.19)	Observed < expected

Table 47 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)	
CVST+TCP:80 +	42	0	3509828	2	0	Inf (Inf - Inf)	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

[b] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

CI Confidence interval; CVST Cerebral Venous Sinus Thrombosis; EU European Union; TCP Thrombocytopenia; UK United Kingdom

Fatal cases

Eighteen percent (245 out of 1375) cases reported fatal outcome, age and gender, case classification by dose 1 and dose 2 for fatal reports is presented in Table 48, TTS Case Reports by age/gender, and fatality.

Table 48 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

Age Group	Confirmed			Probable			Possible			Unlikely		Criteria not met			Total
	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	
All Doses															
Age - 18-29 Yrs	6 (1)	12 (2)	0 (0)	11 (2)	3 (1)	0 (0)	18 (1)	17 (4)	0 (0)	0 (0)	0 (0)	14 (1)	17 (2)	0 (0)	98 (14)
Age - 30-39 Yrs	17 (6)	10 (2)	0 (0)	15 (3)	10 (7)	0 (0)	32 (7)	15 (4)	0 (0)	0 (0)	0 (0)	37 (7)	19 (4)	0 (0)	155 (40)
Age - 40-49 Yrs	28 (4)	21 (1)	0 (0)	35 (8)	19 (1)	0 (0)	33 (13)	30 (0)	0 (0)	0 (0)	0 (0)	44 (9)	27 (5)	0 (0)	237 (41)
Age - 50-59 Yrs	17 (5)	19 (3)	0 (0)	32 (7)	31 (4)	2 (0)	63 (10)	36 (4)	1 (1)	0 (0)	0 (0)	35 (7)	29 (7)	0 (0)	265 (48)
Age - 60-69 Yrs	9 (3)	14 (1)	0 (0)	26 (5)	28 (7)	0 (0)	74 (19)	38 (2)	0 (0)	0 (0)	3 (1)	51 (9)	45 (7)	1 (0)	289 (54)
Age - 70-79 Yrs	6 (0)	3 (3)	0 (0)	14 (2)	12 ()	0 (0)	25 (4)	35 (2)	0 (0)	1 (1)	0 (0)	31 (3)	31 (3)	1 (0)	159 (18)
Age - 80+ Yrs	0 (0)	0 (0)	0 (0)	6 (3)	6 (2)	0 (0)	11 (1)	11 (1)	0 (0)	0 (0)	0 (0)	12 (2)	14 (4)	0 (0)	60 (13)

Table 48 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

Age Group	Confirmed			Probable			Possible			Unlikely		Criteria not met			Total
	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	
Age Unknown	11 (1)	(0)	1 (0)	11 (2)	8 (1)	0 (0)	10 (1)	15 (2)	2 (0)	0 (0)	0 (0)	14 (3)	10 (3)	30 (4)	112 (17)
Grand Total	**94 (20)**	**79 (12)**	**1 (0)**	**150 (32)**	**117 (23)**	**2 (0)**	**266 (56)**	**197 (19)**	**3 (1)**	**1 (1)**	**3 (1)**	**238 (41)**	**192 (35)**	**32 (4)**	**1375 (245)**
Dose 1															
Age - 18-29 Yrs	6 (1)	12 (2)	0 (0)	11 (2)	3 (1)	0 (0)	18 (1)	15 (4)	0 (0)	0 (0)	0 (0)	14 (1)	17 (2)	0 (0)	96 (14)
Age - 30-39 Yrs	17 (6)	10 (2)	0 (0)	15 (3)	10 (7)	0 (0)	32 (7)	14 (4)	0 (0)	0 (0)	0 (0)	37 (7)	19 (4)	0 (0)	154 (40)
Age - 40-49 Yrs	28 (4)	21 (1)	0 (0)	33 (8)	18 (1)	0 (0)	32 (13)	26 (0)	0 (0)	0 (0)	0 (0)	44 (9)	26 (5)	0 (0)	228 (41)
Age - 50-59 Yrs	17 (5)	19 (3)	0 (0)	31 (7)	30 (4)	2 (0)	62 (10)	35 (3)	1 (1)	0 (0)	0 (0)	34 (7)	27 (7)	0 (0)	258 (47)
Age - 60-69 Yrs	9 (3)	14 (1)	0 (0)	25 (5)	27 (7)	0 (0)	70 (19)	35 (2)	0 (0)	0 (0)	3 (1)	50 (8)	45 (7)	1 (0)	279 (53)

Table 48 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

Age Group	Confirmed			Probable			Possible			Unlikely		Criteria not met			Total
	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	
Age - 70-79 Yrs	6 ()	1 (1)	0 (0)	13 (2)	9 ()	0 (0)	23 (3)	28 (1)	0 (0)	1 (1)	0 (0)	28 (3)	31 (3)	1 (0)	141 (14)
Age - 80+ Yrs	0 (0)	0 ()	0 (0)	5 (3)	3 (1)	0 (0)	7 (1)	10 (1)	0 (0)	0 (0)	0 (0)	11 (2)	14 (4)	0 (0)	50 (12)
Age Unknown	11 (1)	0 ()	1 (0)	8 (2)	7 (1)	0 (0)	10 (1)	11 (2)	1 (0)	0 (0)	0 (0)	14 (3)	9 (3)	30 (4)	102 (17)
Grand Total	**94 (20)**	**77 (10)**	**1 (0)**	**141 (32)**	**107 (22)**	**2 (0)**	**254 (55)**	**174 (17)**	**2 (1)**	**1 (1)**	**3 (1)**	**232 (40)**	**188 (35)**	**32 (4)**	**1308 (238)**
Dose 2															
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)
Age - 30-39 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Age - 40-49 Yrs	0 (0)	0 (0)	0 (0)	2 (0)	1 (0)	0 (0)	1 (0)	4 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	9 (0)

Table 48 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

Age Group	Confirmed			Probable			Possible			Unlikely		Criteria not met			Total
	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	F N (Fatal)	M N (Fatal)	F N (Fatal)	M N (Fatal)	Unk N (Fatal)	
Age - 50-59 Yrs	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	2 (0)	0 (0)	7 (1)
Age - 60-69 Yrs	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	4 (0)	3 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	10 (1)
Age - 70-79 Yrs	0 (0)	2 (2)	0 (0)	1 (0)	3 (0)	0 (0)	2 (1)	7 (1)	0 (0)	0 (0)	0 (0)	3 (0)	0 (0)	0 (0)	18 (4)
Age - 80+ Yrs	0 (0)	0 (0)	0 (0)	1 (0)	3 (1)	0 (0)	4 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	10 (1)
Age Unknown	0 (0)	0 (0)	0 (0)	3 (0)	1 (0)	0 (0)	0 (0)	4 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	10 (0)
Grand Total	0 (0)	2 (2)	0 (0)	9 (0)	10 (1)	0 (0)	12 (1)	23 (2)	1 (0)	0 (0)	0 (0)	6 (1)	4 (0)	0 (0)	67 (7)

F Female, M Male, N Number of case reports, Unk-Gender Unknown.

Time to onset was available in 218 of the 245 fatal reports and ranged from 1 day to 104 days. Median TTO in fatal reports was 11 days. In 7 fatal case reports the TTS events were reported after Dose 2; TTO was available all 7 reports and median TTO was 11 days (range 2 to 27 days).

Most frequently reported site of thrombosis in fatal reports was Cerebral venous sinus thrombosis (74), followed by (>10) Pulmonary embolism (46), Thrombosis (39), Cerebral venous thrombosis (24), Portal vein thrombosis (23), Hemiparesis (21), Disseminated intravascular coagulation (20), Cerebral thrombosis (17), Superior sagittal sinus thrombosis (16), Cerebrovascular accident (12), Ischaemic stroke (12), Deep vein thrombosis (DVT) (12). The HLT of Cerebrovascular venous and sinus thrombosis 121 (49.4%) [Cerebral venous sinus thrombosis (74), Cerebral venous sinus thrombosis (24), Superior sagittal sinus thrombosis (16), Transverse sinus thrombosis (5), Cavernous sinus thrombosis (2),] represents the most common sites in fatal reports.

In 43 fatal case reports, PTs related to Embolic and thrombotic events, arterial (SMQ) were reported, which included following PTs: Ischaemic stroke (12), Aortic thrombosis (8), Arterial thrombosis (6), Carotid artery thrombosis (6), Peripheral artery thrombosis (4), Acute myocardial infarction (4), Thrombotic thrombocytopenic purpura (4), Cerebral artery occlusion (4), Myocardial infarction (3), Coronary artery thrombosis (2), Peripheral artery occlusion (1), Mesenteric artery thrombosis (1), Renal artery occlusion (1), Hepatic artery thrombosis (1), Transient ischaemic attack (1), Iliac artery occlusion (1), and Ischaemic cerebral infarction (1).

167 case reports contained PTs related to Embolic and thrombotic events, venous (SMQ), which included following PTs: Cerebral venous sinus thrombosis (74), Pulmonary embolism (46), Cerebral venous thrombosis (24), Portal vein thrombosis (23), Superior sagittal sinus thrombosis (16), DVT (12), Mesenteric vein thrombosis (9), Splenic vein thrombosis (7), Transverse sinus thrombosis (5), Visceral venous thrombosis (5), Hepatic vein thrombosis (4), Jugular vein thrombosis (4), Pulmonary thrombosis (4), Renal vein thrombosis (2), Vena cava thrombosis (2), Thrombophlebitis (2), Cavernous sinus thrombosis (2), Ovarian vein thrombosis (1), Venoocclusive liver disease (1), Retinal vein thrombosis (1), Pelvic venous thrombosis (1), Venous thrombosis (1), Portal vein occlusion (1), Venous thrombosis limb (1), Budd-Chiari syndrome (1), and Portosplenomesenteric venous thrombosis (1).

122 case reports contained PTs related to Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ), which included following PTs: Thrombosis (39), Hemiparesis (21), Disseminated intravascular coagulation (20), Cerebral thrombosis (17), Cerebrovascular accident (12), Haemorrhagic stroke (9), Cerebral infarction (7), Hemiplegia (7), Embolism (6), Heparin-induced TCP (5), Splenic infarction (4), Cerebral ischaemia (3), Thrombosis mesenteric vessel (3), Infarction (3), Splenic thrombosis (2),

Haemorrhagic cerebral infarction (2), Intestinal infarction (2), Haemorrhagic transformation stroke (2), Cardiac ventricular thrombosis (1), Thrombotic stroke (1), Thrombosis in device (1), Haemorrhagic infarction (1), Adrenal thrombosis (1), Embolic stroke (1), Haemorrhagic adrenal infarction (1), Intracardiac thrombus (1), Brain stem infarction (1), Renal infarct (1), Hepatic infarction (1), Renal vascular thrombosis (1).

In 118 of the 245 fatal case reports reported multiple site of thrombosis; and in 127 of the 245 fatal case reports, there was only one site of thrombosis. In 7 case reports, there was a reported PT from all 3 arterial, venous and vessel type unspecified and mixed arterial and venous SMQ; in 73 case reports, there was 2 vessel type involved.

In 169 out of 245 fatal reports (69%), there was a co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)-Narrow. Most common (≥4) bleeding events included Cerebral haemorrhage (89), Subarachnoid haemorrhage (21), Haemorrhage intracranial (18), Haemorrhagic stroke (9), Haemorrhage (7), Cerebral haematoma (6), Thrombotic thrombocytopenic purpura (4). Thirty case reports had the co-reported events from HLT of Coagulopathies (including 20 cases with disseminated intravascular coagulation).

Fatality/survival rate over time

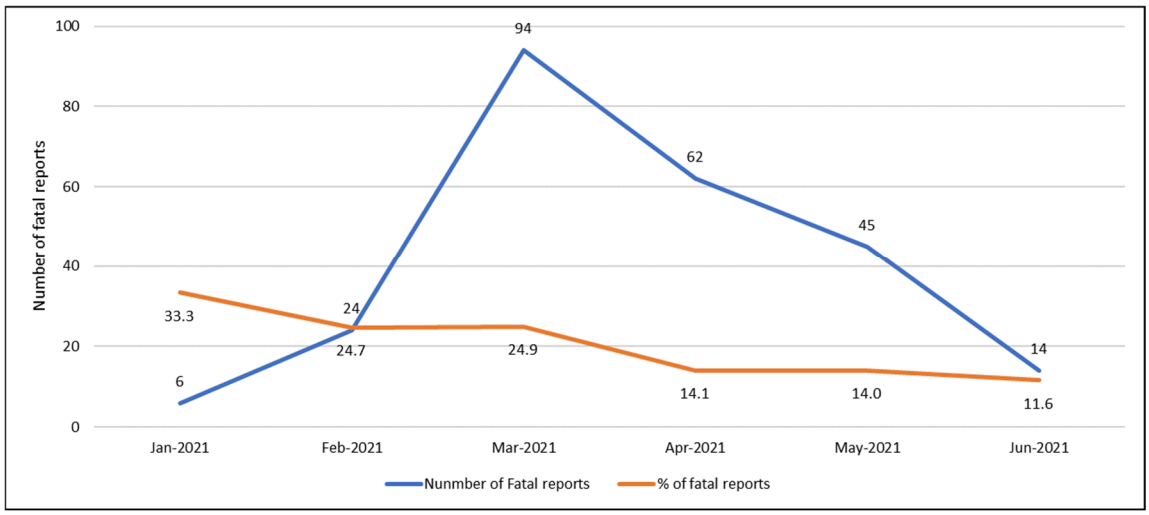
Fatality/survival rate over time was calculated based on the case onset date, however in 172 of the 1375 case reports case onset date was not available. In cases where onset date was not available, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. Fatality/survival rate cumulatively up to 28 June 2021 is presented in Table 49 and Figure 2. Number and percentage of fatal reports since April 2021 are decreasing compared to January 2021-March 2021.

Table 49 TTS fatality/survival rate over time

Month	Number of non-fatal reports	Number of Fatal reports	Total Reports	% of fatal reports
January 2021	12	6	18	33.3
February 2021	73	24	97	24.7
March 2021	283	94	377	24.9
April 2021	379	62	441	14.1
May 2021	276	45	321	14.0
June 2021	107	14	121	11.6
Grand Total	**1130**	**245**	**1375**	**17.8**

TTS Thrombocytopenia Syndrome.

Figure 2 TTS fatality/survival rate over time



TTS reports after Dose 2 of AZD1222

A search of the AstraZeneca global safety database was undertaken to retrieve AE 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 June 2021, including processes and unprocessed cases. 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 67 confirmed cases of TTS following the second dose of COVID-19 VACCINE ASTRAZENECA. Time to onset was available in 63 (94%) of the 67 cases and ranged from 1 to 46 days; median TTO was 10 days after 2nd dose. In 63% (40 out of 63 reports) of the case reports, the TTS events occurred within 14 days after dose 2; 81 % (51 out of 63) and 98 % (62 out of 63) of the case reports were reported within 21 days and 42 after dose 2 respectively.

Of the 67 patients, majority were male (58.2 %; 39 cases), 27 were female (40.3%), and gender was unknown in 1 (1.5%) report. Age ranged from 27 – 95 years with age not provided in 10 of the reports. Median age was 69 years and 38 (67%) of the reports were in vaccinees > 60 years. Outcome in 25 cases were reported as not recovered, 1 recovered, 29 patients recovering, 7 with fatal, 2 reported as recovered with sequalae and outcome unknown in 3 report.

These events included the following sites of thrombosis and most of them were venous site, followed by unspecified and mixed arterial and venous:

Embolic and thrombotic events, venous: Pulmonary embolism (35), DVT (11), Cerebral venous sinus thrombosis (5), Portal vein thrombosis (4), Mesenteric vein thrombosis (2), Cerebral venous thrombosis (2), Jugular vein thrombosis (2), Pelvic venous thrombosis (2), Visceral venous thrombosis (1), Venous thrombosis (1), Pulmonary infarction (1), and Retinal vein occlusion (1).

Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ): Thrombosis (7), Cerebrovascular accident (5), Embolism (5), Intracardiac thrombus (1), Thrombotic stroke (1), Cerebral thrombosis (1), Vascular stent thrombosis (1), Hemiparesis (1), Atrial thrombosis (1), and Haemorrhagic cerebral infarction (1).

Embolic and thrombotic events, arterial: Cerebral artery thrombosis (2), Aortic embolus (1), Peripheral artery thrombosis (1), and Myocardial infarction (1).

Using an estimated exposure 38854532 of people who have received the dose 2 of COVID-19 VACCINE ASTRAZENECA in EU, UK, Philippines, and Australia the reporting rate of thrombotic events in combination with thrombocytopenia (with time to onset ≤ 21 days; 51 reports) following the second COVID-19 VACCINE ASTRAZENECA was estimated to be 1.31 per million doses. Majority of the vaccines who experienced TTS events post Dose 2 were male (58.2%) and were much older (median age 69 years). The rate of TTS following the dose 2 of COVID-19 VACCINE ASTRAZENECA is less compared to the background rate (>65 years) of 23.48 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 51.09 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm [with updated OHDSI-aligned code lists and washout periods]).

This rate of thrombotic events in combination with thrombocytopenia following second vaccine is below the estimated reporting rate of 13.89 per million doses for first dose of COVID-19 VACCINE ASTRAZENECA (961 identified reports with time to onset ≤ 21 days; estimated exposure 69183654 administered doses). Thrombosis with thrombocytopenia syndrome events following the second dose had a different demographic pattern as well, being older and more likely male.

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 (58% vs 43%) and were older (69 years vs. 55 years) compared to first dose recipients. The median time to onset was similar (10 days vs 12 days).

The highest number of fatal reports (49%) were for (CVST- HLT of Cerebrovascular venous and sinus thrombosis).

The highest number of cases were reported from UK (49%) while it received 11.7% of the total worldwide doses.

The most common confounding factors in descending order of frequency in all 1375 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.

Conclusion

Thrombosis in combination with thrombocytopenia/ TTS is considered appropriately described in the COVID-19 VACCINE ASTRAZENECA CDS (Sections 4.3, 4.4, and 4.8). 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.

Thrombosis in combination with thrombocytopenia/ TTS is an Important Identified Risk to the Core and EU RMP and the topic will continue to be kept under close surveillance by AstraZeneca.

Additional information regarding this Important Identified Risk can be found in Section 16.4.1.1.

16.3.3 New information on other potential risks not categorised as important

The AESIs for the COVID-19 VACCINE ASTRAZENECA and associated PTs are listed in Appendix 7.

AESIs listed in Appendix 7 for the COVID-19 VACCINE ASTRAZENECA have been have been included for review in Section 16.3 of this PBRER (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 Outcomes-Neonates as an AESI not included elsewhere in this PBRER. Discussions of any trends, signals, or updates to labels or RMPs are contained within these respective sections of this PBRER document.

16.3.3.1 Pregnancy Outcome - Neonates

Pregnancy outcome – Neonates is currently kept under close surveillance by AstraZeneca.

During the period covered by this PBRER 31 events were reported for the AESI concept of Pregnancy outcome – Neonates:

- Anencephaly (1): PPD-Year-old PPD vaccinee
- Arnold-Chiari malformation (1): PPD-year-old PPD vaccinee
- Arteriovenous malformation (1): (age unspecified) PPD vaccinee
- Choanal atresia (1): PPD-year-old PPD vaccinee
- Coarctation of the aorta (1):
  - PPD : PPD-year-old PPD vaccinee; The vaccinee received the vaccine on PPD during the PPD On an unknown date, experienced PT: Coarctation of the aorta (As reported: PPD has coarctation of the aorta). A foetal cardiac scan was conducted. The event of coarctation of aorta was ongoing.
- Congenital arterial malformation (2): Two PPD-year-old PPD vaccinees
- Congenital diaphragmatic hernia (1): PPD-year-old PPD vaccinee
- Congenital hydrocephalus (1): PPD-year-old PPD vaccinee
- Cystic lymphangioma (1): PPD-year-old PPD vaccinee
- Dysmorphism (2): PPD-year-old PPD and PPD-year-old PPD vaccinees
- Encephalocele (1): PPD-year-old (gender unspecified) vaccinee
- Foetal malformation (3): PPD-year-old PPD and two PPD-year-old PPD vaccinees
- Haemorrhagic arteriovenous malformation (1): PPD-year-old PPD
- Heterotaxia (2): PPD-year-old PPD vaccinee and PPD vaccinee of unknown age
- Limb reduction defect (2): PPD-year-old PPD and PPD-year-old PPD vaccinees
- Neural tube defect (1)
  - PPD : PPD a PPD-Year-old PPD . The PPD received COVID-19 VACCINE ASTRAZENECA (chadox1 ncov-19) on PPD . On an unknown date, the patient experienced PPD . On an unknown date, foetus of PPD experienced neural tube defect. It was unknown if any action was taken with COVID-19

VACCINE ASTRAZENECA. The foetus of PPD died from the event of neural tube defect on PPD.

- Premature baby (1):
  - PPD: PPD-year-old PPD vaccinee. The vaccinee was vaccinated during the PPD. The vaccinee experienced light-headedness, severe nausea, and nearly fainted the same day as vaccination. The next day, PPD experienced PPD. Scans showed no anomalies or complications.
- Pyloric stenosis (1): PPD-year-old PPD vaccinee
- Stillbirth (2):
  - PPD: PPD-year-old PPD vaccinee. The vaccinee experienced a stillbirth 46 days after vaccination (PPD). The vaccinee experienced PPD and streptococcal infection on unknown dates.
  - PPD: PPD-year-old-PPD vaccinee. The vaccinee received both doses PPD; first dose at PPD and the second dose at PPD. On an unknown dates, the vaccinee experienced pre-eclampsia and low weight. At PPD, the vaccinee had a stillbirth.
- Transposition of the great vessels (1): PPD-year-old PPD vaccinee
- Vascular malformation (3): PPD-year-old-PPD, PPD-year-old PPD, and PPD-year-old PPD vaccinees.
- Ventricular septal defect (1):
  - PPD: PPD-year-old PPD vaccinee. Patient received COVID-19 VACCINE ASTRAZENECA (chadox1 ncov-19) during PPD (PPD). On PPD, the patient experienced PPD. On an unknown date, the patient experienced PPD. On an unknown date, the patient experienced PPD (Ventricular septal defect).

Upon further review, 25 of these cases (excluding case PPD and PPD) were acquired conditions and not congenital malformations. Two cases (PPD) were suggestive of congenital malformation. Case PPD was considered under AESI-Pregnancy outcome-maternal due to the event of "Spontaneous abortion".

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship between Pregnancy outcome – Neonates and COVID-19 VACCINE ASTRAZENECA could be established.

The topic will continue to be kept under close surveillance by AstraZeneca.

16.3.4 New information on other identified risks not categorised as important

16.3.4.1 Reactogenicity

A cumulative search of the AstraZeneca global safety database through 28 June 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, Arthralgia, Injection site bruising, Injection site pain, Injection site pruritus, Injection site swelling, Injection site warmth, Injection site erythema, Fatigue, Malaise, Chills and Pyrexia.

A total of 750858 cases involving 775699 events of reactogenicity were identified from the global safety database. Of these 750858 cases, there were 18972 serious, medically confirmed cases of reactogenic events with COVID-19 ASTRAZENECA VACCINE. Of the 18972 cases, 14636 (77%) occurred in females, 3993 (21%) in males, and 343 (2%) of unknown gender. Of these 18972 cases, the distribution of the reactogenic events were as follows: Headache (4391 events), Pyrexia (4046 events), Chills (3600 events), Fatigue (1808 events), Nausea (1800 events), Myalgia (1800 events), Arthralgia (1261 events), Malaise (1239 events), Vomiting (1174 events), Injection site pain (598 events), Injection site erythema (144 events), Injection site swelling (52 events), Injection site pruritus (27 events), Injection site warmth (26 events), and Injection site bruising (1 event).

The current COVID-19 VACCINE ASTRAZENECA Summary of Product Characteristics (SmPC) lists the frequency of all of the reactogenic events used for this analysis as either common (>1/100 to <1/10) or very common (>1/10) based on clinical trial data. AstraZeneca maintains confidence in these frequency estimates currently.

16.3.5 Update on missing information

All concepts considered as missing information in the Core RMP are provided in Section 16.1 included in Table 50 below.

Table 50 Risks presented in Core RMP (Version 3; dated 28 April 2021)

Section/Topic	Core RMP
Missing Information	• Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women

Table 50 Risks presented in Core RMP (Version 3; dated 28 April 2021)

Section/Topic	Core RMP
	• 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

COVID-19 Coronavirus Disease 2019, RMP Risk Management Plan.

16.3.5.1 Use of COVID-19 VACCINE ASTRAZENECA in pregnancy and breastfeeding women/Use during pregnancy and while breastfeeding

There is a limited amount of data from the use of COVID-19 VACCINE ASTRAZENECA in pregnancy and/or lactating women, or from women who become pregnant after receiving COVID-19 VACCINE ASTRAZENECA. While preliminary non-clinical safety studies have not indicated any concern to date, the effect of COVID-19 VACCINE ASTRAZENECA on the foetus and breastfed infant is unknown, as data are currently insufficient to inform on any vaccine-associated risk.

During the period covered by this PBRER, there were 347 case reports with 1476 adverse reactions involving pregnant women. Upon review of these 347 cases, there are 338 cases with pregnancies and 9 cases without pregnancies. There were 48 case reports of Abortion spontaneous. Further details of case reports of Abortion spontaneous are provided in Table 51.

Table 51 Summary of Spontaneous Abortion (n = 48) with COVID-19 VACCINE ASTRAZENECA reported during the review period (29 December 2020 to 28 June 2021)

Case ID	Case details
PPD	A PPD-year-old with a history of PPD Vaccination occurred prior to pregnancy and miscarriage 70 days after vaccination
PPD	A PPD-year-old who experienced a miscarriage during the PPD days after vaccination
PPD	A PPD-year-old who experienced a miscarriage at PPD, 8 weeks after receiving the second dose.
PPD	A PPD-year-old who experienced a miscarriage at PPD, 45 days after vaccination
PPD	A PPD-year-old who experienced a miscarriage on an unknown date after vaccination
PPD	A PPD-year-old who experienced a miscarriage during the PPD, less than 2 months after vaccination

Table 51 Summary of Spontaneous Abortion (n = 48) with COVID-19 VACCINE ASTRAZENECA reported during the review period (29 December 2020 to 28 June 2021)

Case ID	Case details
PPD	A PPD-year-old who experienced a miscarriage 55 days after receiving the first dose.
PPD	A PPD-year-old who experienced a miscarriage 51 days after vaccination.
PPD	A PPD-year-old who experienced a miscarriage during the PPD, one day after vaccination.
PPD	A PPD-year-old who experienced a miscarriage during the PPD, 22 days after vaccination.
PPD	A PPD-year-old with a history of PPD experienced a miscarriage during the PPD on an unknown date after vaccination.
PPD	A PPD-year-old who experienced a miscarriage on an unknown date. Vaccination occurred prior to pregnancy.
PPD	A PPD-year-old who experienced a miscarriage 1 day after receiving the second dose during the PPD.
PPD	A PPD-year-old who experienced a miscarriage during the PPD, 21 days after receiving the second dose.
PPD	A PPD-year-old who experienced a miscarriage on an unknown date after vaccination.
PPD	A PPD-year-old who experienced a miscarriage 92 days after vaccination with COVID-19 VACCINE ASTRAZENECA and 2 days after vaccination with mRNA VACCINE BIONTECH.
PPD	A PPD-year-old who experienced a miscarriage during the PPD on an unknown date after receiving the second dose.
PPD	A PPD-year-old who experienced a miscarriage during the PPD, one day after vaccination.
PPD	A PPD-year-old who experienced a miscarriage 33 days after vaccination during the PPD.
PPD	A PPD-year-old with a history of PPD experienced a miscarriage 45 days after vaccination.
PPD	A PPD-year-old who experienced a miscarriage 36 days after vaccination during the PPD.
PPD	A PPD-year-old who experienced a miscarriage 3 days after receiving the second dose.
PPD	A PPD-year-old who experienced a miscarriage on an unknown date after vaccination.
PPD	A PPD-year-old who experienced a miscarriage 52 days after vaccination.

Table 51 Summary of Spontaneous Abortion (n = 48) with COVID-19 VACCINE ASTRAZENECA reported during the review period (29 December 2020 to 28 June 2021)

Case ID	Case details
PPD	A vaccinee of unknown age was unaware of the pregnancy when receiving the vaccine. One day after vaccination, PPD experienced events of Influenza like illness, Hypertension, and Abortion spontaneous.
PPD	A PPD-year-old vaccinee previously had PPD . Vaccinee experienced a high fever 12 hours after receiving the vaccine during the PPD of pregnancy and Abortion spontaneous 2 days later.
PPD	Involved a vaccinee of unknown age who experienced pregnancy loss 44 days after vaccination
PPD	Involved a PPD-year-old who experienced Abortion spontaneous 18 days after vaccination
PPD	Involved a PPD-year-old who experienced a miscarriage during the PPD , one day after vaccination
PPD	Involved a PPD-year-old with PPD who experienced pregnancy loss with a PPD the same month as vaccination
PPD	Involved a PPD-year-old who experienced loss of pregnancy on an unknown date after vaccination during the PPD . The vaccinee presented at 18 weeks with PPD
PPD	A PPD-year-old who experienced a miscarriage during the PPD 56 days after vaccination
PPD	A PPD-year-old who experienced a miscarriage at 8 weeks 10 days after vaccination
PPD	Involved a PPD-year-old who experienced an PPD miscarriage 3 days after vaccination during the PPD
PPD	Involved a PPD-year-old with a history of PPD , who experienced a miscarriage 29 days after vaccination
PPD	Involved a PPD-year-old who experienced a miscarriage 49 days after vaccination during the PPD
PPD	Involved a PPD-year-old who experienced a miscarriage 37 days after vaccination
PPD	Involved a PPD-year-old with who experienced a miscarriage 33 days after vaccination during the PPD
PPD	Involved a PPD-year-old who experienced a miscarriage 22 days after vaccination
PPD	A PPD-year-old who experienced a miscarriage at PPD . Vaccination occurred prior to pregnancy
PPD	A PPD-year-old who experienced an early miscarriage 9 days after vaccination
PPD	A PPD-year-old who experienced pregnancy loss at PPD gestation on an unknown date after vaccination

Table 51 Summary of Spontaneous Abortion (n = 48) with COVID-19 VACCINE ASTRAZENECA reported during the review period (29 December 2020 to 28 June 2021)

Case ID	Case details
PPD	A PPD-year-old with a history of PPD experienced a miscarriage on an unknown date after vaccination
PPD	A vaccinee of unknown age who experienced a miscarriage at PPD, over a month after vaccination
PPD	A PPD-year-old who experienced a miscarriage 31 days after vaccination during the PPD
PPD	A PPD-year-old who experienced an PPD miscarriage. Vaccination occurred 1 week prior to pregnancy and miscarriage over a month after vaccination.
PPD	A PPD-year-old with a history of PPD experienced a miscarriage 25 days after receiving the second dose. The vaccinee discovered PPD was pregnant following exposure to the second dose.
PPD	A PPD-year-old who experienced a miscarriage a few days prior to vaccination, as PPD was no longer pregnant

COVID-19 Coronavirus Disease 2019, mRNA Messenger Ribonucleic Acid, n Number.

There was one case (PPD) of PPD abortion involving a PPD-year-old who experienced an PPD at PPD on an unknown date after vaccination with first dose. At the time of vaccination, the vaccinee had a UTI and was being treated with PPD. The vaccinee experienced PPD and sensation of PPD on unknown dates. At the time of the report, it was unknown if the abortion had already occurred.

There was one case (PPD) of PPD involving a vaccinee of unknown age. The vaccinee received both doses during pregnancy; first dose at PPD and the second dose at PPD. At PPD, the vaccinee had a PPD. Events of PPD were also reported on unknown dates. There have been no other significant updates to this case received during the reporting period.

There was one case (PPD) of Abortion PPD involving a PPD year-old vaccinee. Thirty-nine days after vaccination, the PPD

There were two cases (PPD) of PPD. Case PPD involved a PPD-year-old who was recommended vaccination due to previous PPD. Twelve days after vaccination, the vaccinee experienced PPD Case PPD involved a PPD year-old who experienced PPD four days after

receiving the vaccine. The vaccinee experienced Headache, Fatigue, and Malaise the same day after receiving the vaccine and PPD on an unknown date. It was reported the PPD

Of the remaining 285 cases, event outcomes for pregnancy related PTs were:

- Drug exposure before pregnancy: Unknown (1)
- Ectopic pregnancy: Recovered (1), Recovered with sequelae (1)
  - PPD : A pregnant vaccinee of unknown age experienced PPD pregnancy 22 days after vaccination. The vaccinee recovered from the event after 2 weeks. Maternal risk factors were not reported.
  - PPD : A pregnant vaccinee of unknown age. The vaccinee did not know PPD was in PPD pregnancy when receiving the vaccine and experienced PPD pregnancy that needed PPD , on an unknown date.
- Exposure during pregnancy: Unknown pregnancy outcome (71), Died (1)
  - PPD : A pregnant vaccinee of unknown age received the vaccine on an unknown date. On an unknown date, PPD experienced thrombosis and died on an unknown date. Cause of death was unknown.
- Foetal exposure during pregnancy: Unknown (5)
- Maternal exposure before pregnancy: Unknown (4)
- Maternal exposure during pregnancy: Unknown (179), Recovered (2), Not recovered (2)
  - PPD : A vaccinee of unknown age received the vaccine during pregnancy and recovered from the event on an unknown date.
  - PPD : A PPD -year-old received the vaccine during pregnancy and recovered from the event on an unknown date.
  - PPD : A vaccinee of unknown age received the vaccine during pregnancy and the event was ongoing at the time of reporting.
  - PPD : A PPD -year-old vaccinee received the vaccine during the PPD . The same day as vaccination, PPD experienced Feeling hot, Pain in extremity, Injection site reaction, Headache, Fatigue, and Myalgia. The vaccinee recovered from these events the next day. The event of Maternal exposure during pregnancy was ongoing at the time of reporting.
- Maternal exposure timing unspecified: Not recovered (1)
  - PPD : A PPD -year-old discovered PPD was pregnant on an unknown date after receiving the first dose. At the time of the report, the vaccinee was PPD PPD pregnant (event ongoing) and has cancelled the second dose.
- Morning sickness: Recovered (1)
  - PPD : A PPD -year-old vaccinee experienced vomiting in pregnancy 1 day after vaccination. The vaccinee recovered from the event after 2 weeks. Outcome of pregnancy is unknown.
- Placental infarction: Not recovered (1)

  - PPD : A PPD -year-old experienced PPD 52 days prior to vaccination. The event was ongoing at the time of reporting.
- Pregnancy: Unknown (9), Recovering (1), Recovered (1), Not recovered (1)
  - PPD : A vaccinee of unknown age received the second dose at PPD PPD . Pregnancy scan was normal, and at the time of reporting, the event was improving.
  - PPD : A PPD -year-old vaccinee experienced pregnancy on an unknown date. At the time of reporting, the event was ongoing.
  - PPD : A PPD -year-old vaccinee received the first dose and subsequently found out PPD was PPD pregnant at that time. PPD reported this when attending for PPD second vaccination. After informed discussion with the obstetrician, PPD wished to proceed with PPD second vaccination and received the second dose at PPD .
- Pregnancy after post coital contraception: Unknown (1)
- Pregnancy test: Recovered (1)
- Pregnancy test positive: Unknown (1)

Pregnancy cases according to country of origin are presented below in Table 52.

Table 52 Pregnancy cases according to country of origin

Country	Total
United Kingdom	240
Mexico	13
Poland	12
Brazil	10
Germany	9
Italy	6
Belgium	5
Spain	5
Netherlands	4
Portugal	4
France	4
Australia	4
Ireland	3
Romania	2
Bulgaria	2
Hungary	2
India	2
[redacted]	1

Table 52 Pregnancy cases according to country of origin

Country	Total
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1
[redacted]	1

Conclusion

This cumulative review of the Use of COVID-19 VACCINE ASTRAZENECA during pregnancy or while breastfeeding did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern.

From the data identified during the reporting period Use in pregnancy and while breastfeeding will continue to be considered missing information for COVID-19 VACCINE ASTRAZENECA and included in the Core and EU RMPs.

As COVID-19 VACCINE ASTRAZENECA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of characterizing the safety profile in this population, is considered necessary.

Further study and characterization of the use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women will be investigated in the ongoing PASS activities.Refer to Appendix 4 for additional details.

Additional information regarding the use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women 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 this population receiving COVID-19 VACCINE ASTRAZENECA will be different than that of the general population, given the paucity of data, the possibility cannot be excluded.

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in patients identified as immunocompromised. Immune compromised patients were identified in the Global Safety Database through a coded medical history search of the High Level Term: Immune and associated conditions NEC.

The search of the AstraZeneca global safety database identified a cumulative total of 9243 cases (94.2% spontaneous cases, 5.7% non-interventional/post marketing cases, and 0.1% literature) for the topic use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency/Use in immunocompromised patients.

Of the 9243 cases , 74.6% of were reported in females and 22.5% were in males. Gender was not reported in the remaining 2.9% of cases. Age ranged from 18 years to <65 years in 78.0% of the reports, 65+ Years in 14.5% , and 0.5% in less than 18 years of age. Age was not reported in the remaining 6.6% of cases. The majority of reports (89.9%) were not medically confirmed with the remaining 10.1% being medically confirmed.

Of these 9243 cases, 6800 (73.6%) were considered serious and 2443 (26.4%) non serious. The outcome was fatal in 57 (0.6%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 8276 of the 9243 cases. Most of the events (66.9%) occurred within one day of vaccination, 15.2% occurred 2-15 days post-vaccination, 4.5% occurred between 16-200 days post-vaccination and another 0.3% occurred >200 days after vaccination and in 13.1% time to onset was unknown.

Outcome was reported in 81.7% of the 9243 cases, with 27.0% reported as Recovered, 22.6% as Recovering, 26.9% Not recovered, and 2.9% as Recovered with sequelae. Outcome was unknown in 18.3% of reports. The top 20 reported PTs are Headache (3729), Pyrexia (2977), Fatigue (2587), Chills (2120), Nausea (1573), Myalgia (1421), Arthralgia (1230), Dizziness (1106), Pain in extremity (993), Malaise (763), Pain (761), Vomiting (552), Influenza like illness (513), Diarrhoea (504), Tremor (460), Hyperhidrosis (443), Dyspnoea (435), Pruritus (409), Migraine (386) and Rash (369).

Patients on immunosuppressive medications were excluded from COVID-19 studies, so the efficacy of the vaccine in immunosuppressive populations has not been established.

Methotrexate and rituximab have decreased the serological responses to other vaccines. Tentative recommendations have been given to plan the vaccination of the immunocompromised patients to ensure maximum possible seroprotection, including holding methotrexate for 2 weeks after the vaccination and scheduling rituximab a few weeks after the vaccination.

A systematic review on COVID-19 course and outcomes in patients receiving different disease-modifying therapies was conducted. Emerging data on SARS-CoV-2 vaccines was used to elaborate recommendations. Data from 4417 patients suggest that having multiple sclerosis did not predict a higher risk of severe COVID-19, although, as with the general population, advanced age, comorbidities, and higher disability significantly impact COVID-19 outcomes. This analysis showed that most disease modifying therapies have a negligible influence on COVID-19 incidence and outcome. Those causing severe lymphopenia and hypogammaglobulinemia, such as anti-CD20 therapies, appeared to increase hospitalization, worse outcomes and a higher risk of re-infection. Blunted immune responses have been reported for many disease modifying therapies. Clinical evidence did not support an increased risk of multiple sclerosis relapse or vaccination failure, but vaccination timing needs to be individually tailored. For cladribine and alemtuzumab, itis recommended to wait 3–6 months after the last cycle until vaccination. For the general anti-CD20 therapies, vaccination must be deferred toward the end of the cycle and the next dose administered 4 to 6 weeks after completing the vaccine.

Studies have shown immunogenicity and efficacy rates of over 90% in the immunocompetent adult population. immune- mediated inflammatory diseases who may also be on immunomodulatory medications. Patients with immune-mediated inflammatory diseases have been shown to have attenuated immune responses to seasonal influenza vaccination. Patients in this population were observed for humoral and cellular immune response to two doses of BNT162b2 mRNA COVID-19 vaccine in participants with IMID (on immunomodulators) compared with healthy controls.

Individuals with IMID on methotrexate demonstrated up to a 62% reduced rate of adequate immunogenicity to BNT162b2 mRNA vaccination. Those on anticytokine or non-methotrexate oral medications demonstrate similar levels of immunogenicity as healthy controls (greater than 90%). Similarly, vaccination did not induce an activated CD8+ T- cell response in participants on background methotrexate, unlike healthy controls and patients with IMID not receiving methotrexate.

There is still no consensus on whether solid organ transplantation (SOT) recipients with COVID-19 are at greater risk of developing severe or fatal COVID-19. A systematic review and meta-analysis were conducted to investigate the association between SOT, severe

COVID-19 illness, and mortality: A total number of 15 articles with 265,839 participants were included in this study. Among the total number of participants, 1485 were SOT recipients.

The meta-analysis results showed that transplant patients with COVID-19 were remarkably associated with a higher risk of intensive care unit (ICU) admission than non-transplant patients (OR = 1.57, 95%CI: 1.07 to 2.31, P = 0.02). On the other hand, there were no statistically significant differences between SOT recipients and non-SOT recipients in mechanical ventilation need (OR = 1.55, 95%CI: 0.98 to 2.44, P = 0.06). In addition, we found that SOT recipients with COVID-19 had 1.40-fold increased odds of mortality than non-SOT recipients (OR = 1.40, 95%CI: 1.10 to 1.79, P = 0.007). Moreover, pooled analysis of adjusted results revealed that SOT recipients had a greater risk of mortality compared with non-SOT patients [hazard ratio (HR) = 1.54, 95%CI: 1.03 to 2.32, P = 0.037]. The study conclusions were limited by a relatively small sample size, short follow-up period, and the fact that most of the studies included were retrospective in design. The results of this study indicate that SOT recipients with COVID-19 had a more significant risk of COVID-19 severity and mortality than the general population.

Conclusion

This cumulative review of the Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern.

This cumulative review of the Use of COVID-19 VACCINE ASTRAZENECA with other vaccines did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern.

From the data identified during the reporting period, Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency/Use in immunocompromised patients will continue to be considered missing information for COVID-19 VACCINE ASTRAZENECA and included in the core and EU RMPs.

Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency will be investigated in the ongoing PASS activities. Refer to Appendix 4 for additional details.

Additional information regarding the Use of COVID-19 VACCINE ASTRAZENECA in immune compromised individuals 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 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. 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.

A cumulative search of the AstraZeneca Global Safety Database through 28 June 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 mentioned below:

16.3.5.3.1 Frail

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with 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.

The search of the AstraZeneca global safety database identified a cumulative total of 497 cases (97.8% spontaneous cases, 2.2% 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 497 cases ,78.1% of were reported in females and 19.7% were in males. Gender was not reported in the remaining 2.2% of cases. Age ranged from 18 years to <65 years in 53.7% of the reports, 65+ Years in 33.2% , and 0.5% in less than 18 years of age. Age was not reported in the remaining 11.5% of cases. The majority of reports (73.0%) were not medically confirmed with the remaining 27.0% being medically confirmed.

Of these 497 cases, 303 (61.0%) were considered serious and 194 (39.0%) non serious. The outcome was fatal in 83 (16.7%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 366 of the 497 cases. Most of the events (52.4%) occurred within one day of vaccination, 13.3% occurred 2-15 days post-vaccination, 4.8% occurred between 16-200 days post-vaccination and another 0.2% occurred >200 days after vaccination and in 29.2% time to onset was unknown.

Outcome was reported in 92% of the 497 cases, with 23.9% reported as Recovered, 20.1% as Recovering, 30.2% Not recovered, and 1% as Recovered with sequelae. Outcome was unknown in 8% of reports. The top 20 reported PTs are Bedridden (331),Pyrexia (227), Headache (215), Fatigue (160), Chills (142) Nausea (135), Myalgia (99), Dizziness (94), Malaise (90), Asthenia (82), Pain (82), Arthralgia (77), Pain in extremity (68), Vomiting (64), Decreased appetite (57), Dyspnoea (47), Hyperhidrosis (44), Death (42), Diarrhoea (41), Influenza like illness (32).

16.3.5.3.2 Hip Fracture

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Hip fracture.

The search of the AstraZeneca global safety database identified a cumulative total of 19 cases (100% spontaneous 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 Hip fracture.

Of the 19 cases , 73.7% of were reported in females and 26.3% were in males. Age ranged from 18 years to <65 years in 42.1% of the reports, 65+ Years in 57.9%. The majority of reports (78.9%) were not medically confirmed with the remaining 21.1% being medically confirmed.

Of these 19 cases, 13 (68.4%) were considered serious and 6 (31.6%) non serious. The outcome was fatal in 3 (15.8%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 16 of the 19 cases. Most of the events (55.0%) occurred within one day of vaccination, 20.0% occurred 2-15 days post-vaccination, 5% occurred between 16-20 days post-vaccination and in 20.0% time to onset was unknown.

Outcome was reported in 78.6% of the 19 cases, with 32.1% reported as Recovered, 7.1% as Recovering, and 28.6% Not recovered. Outcome was unknown in 21.4% of reports. The top 20 reported PTs are Headache (8), Fatigue (5), Pyrexia (5), Chills (4), Arthralgia (2), DVT (2), Diarrhoea (2), Epistaxis (2), Malaise (2), Myalgia (2), Nausea (2), Pain in extremity (2), Pulmonary embolism (2), TCP (2), Vomiting (2), Abdominal pain (1), Abdominal pain upper (1), Asthenia (1), Balance disorder (1), Condition aggravated (1).

16.3.5.3.3 Cachexia

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE

ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Cachexia.

The search of the AstraZeneca global safety database identified a cumulative total of 86 cases (97.7% spontaneous cases and 2.3% non-interventional/post-market) 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 Cachexia.

Of the 86 cases ,59.3% of were reported in females and 37.2% were in males. Gender was not reported in the remaining 3.5% of cases Age ranged from 18 years to <65 years in 65.1% of the reports, 65+ Years in 24.4%. Age was not reported in the remaining 10.5% of cases The majority of reports (77.9%) were not medically confirmed with the remaining 22.1% being medically confirmed.

Of these 86 cases, 70 (81.4%) were considered serious and 16 (18.6%) non serious. The outcome was fatal in 3 (3.5%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 71 of the 86 cases. Most of the events (58.9%) occurred within one day of vaccination, 13.3% occurred 2-15 days post-vaccination, 6.7% occurred between 16-80 days post-vaccination and in 21.1% time to onset was unknown.

Outcome was reported in 76.7% of the 86 cases, with 26.0% reported as Recovered, 13.3% as Recovering, 31.3% Not recovered and 4.0% as Recovered with sequelae. Outcome was unknown in 23.3% of reports. The top 20 reported PTs are Fatigue (29), Headache (28), Pyrexia (20), Pain in extremity (15), Dizziness (14), Chills (13), Muscle atrophy (13), Paraesthesia (13), Nausea (11), Pain (11) , Arthralgia (10), Hypoaesthesia (10), Malaise (10), Myalgia (9), Influenza like illness (8), Migraine (7), Vomiting (7), Asthenia (6), Back pain (6), and Diarrhoea (6).

16.3.5.3.4 Bladder Incontinence

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title AZD1222_Bladder incontinence.

The search of the AstraZeneca global safety database identified a cumulative total of 2838 cases (96.6% spontaneous cases and 3.4% non-interventional/post-market) 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 AZD1222_Bladder incontinence. One case was received from the literature.

Of the 2838 cases ,68.3% of were reported in females and 29,2% were in males. Gender was not reported in the remaining 2.5% of cases Age ranged from 0 to <18 Years in 0.2% of the reports, 18 to <65 Years in 65.2%, 65+ Years in 26.3%. . Age was not reported in the remaining 7.5% of cases. The age group of adolescent, adult and elderly was 0.8% (age was not specified). The majority of reports (86.9%) were not medically confirmed with the remaining 13.1% being medically confirmed.

Of these 2838 cases, 2170 (76.5%) were considered serious and 668 (23.5%) non serious. The outcome was fatal in 84 (3.0%) of the total case count.

Information on time to onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available in 2451 of the 2838 cases. Most of the events (58.2%) occurred within one day of vaccination, 18.2% occurred 2 15 days post-vaccination, 6.4% occurred between 16-20 days post-vaccination, 0.4% over 1year and in 16.8% time to onset was unknown.

Outcome was reported in 95.8% of the 2838 cases, with 20.8% reported as Recovered, 23.7% as Recovering, 46.8% Not recovered and 1.5% as Recovered with sequelae. Outcome was unknown in 4.2% of reports. The top 20 reported PTs are Headache (1003), Pyrexia (837), Fatigue (702), Chills (556), Nausea (488), Dizziness (346), Arthralgia (331), Myalgia (331), Pain in extremity (322), Malaise (280), Pain (256), Vomiting (222), Diarrhoea (204), Dyspnoea (173), Tremor (170), Paraesthesia (164), Hyperhidrosis (158), Back pain (153), Influenza like illness (145) and Abdominal pain (143).

16.3.5.3.5 Dementia

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title AZD1222_Dementia.

The search of the AstraZeneca global safety database identified a cumulative total of 1466 cases (98.1% spontaneous cases and 1.9% non-interventional/post-market) 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 AZD1222_Dementia.

Of the 1466 cases ,65.5% of were reported in females and 32.6% were in males. Gender was not reported in the remaining 1.9% of cases Age ranged from 0 to <18 Years in 0.2% of the reports, 18 to <65 Years in 48.4%, 65+ Years in 42.6%. Age was not reported in the remaining 7.6% of cases. The age group of adult and elderly was 1.2% (age was not specified). The majority of reports (75.6%) were not medically confirmed with the remaining 24.4% being medically confirmed.

Of these 1466 cases, 1186 (80.9%) were considered serious and 280 (19.1%) non serious. The outcome was fatal in 132 (9.0%) of the total case count.

Information on time to onset from vaccination with COVID 19 VACCINE ASTRAZENECA was available in 1187 of the 1466 cases. Most of the events (51.9%) occurred within one day of vaccination, 18.6% occurred 2 15 days post-vaccination, 7.3% occurred between 16-200 days post-vaccination, 0.5 up to 1 year and in 21.8% time to onset was unknown.

Outcome was reported in 95.2% of the 1466 cases, with 16.1% reported as Recovered, 19.0% as Recovering, 47.6% Not recovered and 3.4% as Recovered with sequelae. Outcome was unknown in 4.8% of reports. The top 20 reported PTs are Headache (459), Fatigue (447), Amnesia (369), Pyrexia (316), Memory impairment (277), Dizziness (238), Confusional state (219), Chills (207), Nausea (194), Cognitive disorder (190), Myalgia (163), Arthralgia (149), Malaise (141), Dyspnoea (116), Pain in extremity (110), Asthenia (93), Disturbance in attention (92), Pain (88), Vomiting (88), and Feeling abnormal (81).

16.3.5.3.6 Long term

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Indicators of frailty_long term.

The search of the AstraZeneca global safety database identified a cumulative total of 433 cases (98.8% spontaneous cases, 1.2% 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_long term.

Of the 433 cases ,66.3% of were reported in females and 31.4% were in males. Gender was not reported in the remaining 2.3% of cases. Age ranged from 18 years to <65 years in 65.4% of the reports and 65+ Years in 23.8% . The age group of adult and elderly was 1.2% (age was not specified). Age was not reported in the remaining 9.7% of cases. The majority of reports (87.1%) were not medically confirmed with the remaining 12.9% being medically confirmed.

Of these 433 cases, 416 (96.1%) were considered serious and 17 (3.9%) non serious. The outcome was fatal in 38 (8.8%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 384 of the 433 cases. Most of the events (50.2%) occurred within one day of vaccination, 22.7% occurred 2-15 days post-vaccination, 10.0% occurred between 16-200 days post-vaccination and another 0.2% occurred over 200 days to 1 year after vaccination and in 16.9% time to onset was unknown.

Outcome was reported in 97% of the 433 cases, with 10.9% reported as Recovered, 21.5% as Recovering, 53.6% Not recovered, and 2.3% as Recovered with sequelae. Outcome was unknown in 3% of reports. The top 20 reported PTs are Headache (145), Fatigue (137), Pyrexia (92), Chills (73), Dizziness (64), Nausea (64), Pain in extremity (61), Arthralgia (54), Myalgia (53), Paraesthesia (50), Dyspnoea (47), Hypoaesthesia (45), Malaise (45), Pain (38), Bell's palsy (33), Influenza like illness (28), Asthenia (27), Hyperhidrosis (27), Muscular weakness (27) and Migraine (26).

16.3.5.3.7 Metastatic Cancer

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title metastatic cancer.

The search of the AstraZeneca global safety database identified a cumulative total of 249 cases (98.4% spontaneous cases, 1.6% 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 metastatic cancer.

Of the 249 cases ,58.6% of were reported in females and 40.2% were in males. Gender was not reported in the remaining 1.2% of cases. Age ranged from 0 to <18 Years in 0.8%, 18 years to <65 years in 54.6% of the reports and 65+ Years in 38.6% . The age group of adult and elderly was 1.5% (age was not specified). Age was not reported in the remaining 4.4% of cases. The majority of reports (63.5%) were not medically confirmed with the remaining 36.5% being medically confirmed.

Of these 249 cases, 222 (89.2%) were considered serious and 27 (10.8%) non serious. The outcome was fatal in 24 (9.6%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 215 of the 249 cases. Most of the events (42.2%) occurred within one day of vaccination, 25.1% occurred 2-15 days post-vaccination, 14.4% occurred between 16-100 days post-vaccination and another 0.8% occurred over 1 year after vaccination and in 18.3% time to onset was unknown.

Outcome was reported in 95.6% of the 249 cases, with 19.7% reported as Recovered, 29.7% as Recovering, 33.7% Not recovered, and 2.8% as Recovered with sequelae. Outcome was unknown in 4.4% of reports. The top 20 reported PTs are Headache (66), Pyrexia (59), Fatigue (46), Chills (35), Nausea (28), TCP (28), Pulmonary embolism (26), Dyspnoea (20), Tremor (19), Myalgia (18), Diarrhoea (17), DVT (16), Influenza like illness (16), Malaise (16), Pain (16), Arthralgia (15), Confusional state (13), Vomiting (13), Dizziness (12) and Hyperhidrosis (12).

16.3.5.3.8 Oxygen (Indicators of frailty_oxygen)

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Indicators of frailty_oxygen.

The search of the AstraZeneca global safety database identified a cumulative total of 1579 cases (99.1% spontaneous cases, 0.6% non-interventional/post marketing cases and 0.3% literature 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_oxygen.

Of the 1579 cases, 61.7% of were reported in females and 36.0% were in males. Gender was not reported in the remaining 2.3% of cases. Age ranged from 0 to <18 Years in 0.4%, 18 years to <65 years in 63.0% of the reports and 65+ Years in 28.3%. The age group of adult and elderly was 0.7% (age was not specified). Age was not reported in the remaining 7.5% of cases. The majority of reports (71.3%) were not medically confirmed with the remaining 28.7% being medically confirmed.

Of these 1579 cases, 1315 (83.3%) were considered serious and 264 (16.7%) non serious. The outcome was fatal in 103 (6.5%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 1310 of the 1579 cases. Most of the events (57.7%) occurred within one day of vaccination, 14.4% occurred 2-15 days post-vaccination, 7.4% occurred between 16-200 days post-vaccination and another 0.3% occurred over 1 year after vaccination and in 20.3% time to onset was unknown.

Outcome was reported in 92.0% of the 1579 cases, with 25.1% reported as Recovered, 25.6% as Recovering, 32.5% Not recovered, and 2.3% as Recovered with sequelae. Outcome was unknown in 8.0% of reports. The top 20 reported PTs are Pyrexia (548), Headache (440), Dyspnoea (405), Fatigue (331), Oxygen saturation decreased (283), Chills (263), Dizziness (237), Nausea (227), Myalgia (179), Malaise (153), Arthralgia (136), Pulmonary embolism (125), Vomiting (117), Chest pain (116), Asthenia (114), Pain (105), Tremor (101), Pain in extremity (97), Cough (93) and Tachycardia (90).

16.3.5.3.9 Palliative

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title PALLIATIVE.

The search of the AstraZeneca global safety database identified a cumulative total of 82 cases (97.6% spontaneous cases and 2.4% literature 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 PALLIATIVE.

Of the 82 cases ,51.2% of were reported in females and 48.8% were in males.. Age ranged from 18 years to <65 years in 24.4% of the reports and 65+ Years in 70.7% . Age was not reported in the remaining 4.9% of cases. The majority of reports (59.8%) were medically confirmed with the remaining 40.2% not medically confirmed.

Of these 82 cases, 79 (96.3%) were considered serious and 3 (3.7%) non serious. The outcome was fatal in 42 (51.2%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 68 of the 82 cases. Most of the events (33.7%) occurred within one day of vaccination, 27.9% occurred 2-15 days post-vaccination, 15.1% occurred between 16-200 days post-vaccination and another 2.3% occurred over 1 year after vaccination and in 20.9% time to onset was unknown.

Outcome was reported in 92.7% of the 82 cases, with 4.9% reported as Recovered, 6.1% as Recovering, 29.3% Not recovered, and 1.2% as Recovered with sequelae. Outcome was unknown in 7.3% of reports. The top 20 reported PTs are Death (12), Malaise (12), Cerebrovascular accident (11), Headache (9), Dyspnoea (8), Syncope (8), Cerebral haemorrhage (7), Pyrexia (7), TCP (7), Myalgia (6), Vomiting (6), Chills (5), Confusional state (5), Facial paralysis (5), Fatigue (5), Nausea (5), Oxygen saturation decreased (4), Pain in extremity (4), Pneumonia (4), Pulmonary embolism (4).

16.3.5.3.10 Pressure Ulcers

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2021 was undertaken to review AEs reported after vaccination with COVID-19 VACCINE ASTRAZENECA in individuals identified in the Global Safety Database through a Standard Search Query for the report title AZD1222_Pressure ulcers.

The search of the AstraZeneca global safety database identified a cumulative total of 2701 cases (97.2% spontaneous cases, 2.8% non-interventional/post marketing cases and 1 literature case) 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 AZD1222_Pressure ulcers.

Of the 2701 cases ,71.4% of were reported in females and 25.8% were in males. Gender was not reported in the remaining 2.8% of cases. Age ranged from 0 to <18 Years in 0.3%, 18 years to <65 years in 74.8% of the reports and 65+ Years in 16.5% . The age group of adult

and elderly was 0.7% (age was not specified). Age was not reported in the remaining 7.6% of cases. The majority of reports (85.0%) were not medically confirmed with the remaining 15.0% being medically confirmed.

Of these 2701 cases, 1724 (63.8%) were considered serious and 977 (36.2%) non serious. The outcome was fatal in 37 (1.4%) of the total case count.

Information on time to onset from vaccination with COVID-19 VACCINE ASTRAZENECA was available in 2334 of the 2701 cases. Most of the events (58.8%) occurred within one day of vaccination, 20.2% occurred 2-15 days post-vaccination, 4.6% occurred between 16-200 days post-vaccination and another 0.3% occurred over 1 year after vaccination and in 16.1% time to onset was unknown.

Outcome was reported in 97.2% of the 2701 cases, with 17.7% reported as Recovered, 22.8% as Recovering, 53.3% Not recovered, and 2.0% as Recovered with sequelae. Outcome was unknown in 2.8% of reports. The top 20 reported PTs are Headache (989), Pyrexia (830), Mouth ulceration (760), Fatigue (710), Chills (555), Nausea (414), Myalgia (397), Arthralgia (313), Dizziness (278), Pain in extremity (262), Malaise (209), Aphthous ulcer (179), Diarrhoea (170), Pain (153), Oropharyngeal pain (142), Vomiting (139), Influenza like illness (129), Pruritus (117), Rash (113) and Lymphadenopathy (106).

Conclusion

This cumulative review of the Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease/Use in frail patients with underlying co-morbidities did not indicate any pattern or cluster suggesting a causal association with COVID-19 VACCINE ASTRAZENECA or a potential safety concern.

From the data identified during the reporting period Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease / Use in frail patients with underlying co-morbidities will continue to be considered missing information for COVID-19 VACCINE ASTRAZENECA and included in the Core and EU RMPs.

Use of COVID-19 VACCINE ASTRAZENECA in patients with severe and/or uncontrolled disease will be investigated in the planned PASS activities. Refer to Appendix 4 for additional details.

Additional information regarding the Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease 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. 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 28 June 2021 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.

Assessment for cases received with Influenza Vaccine:

This search identified a total of 10841 cases (87.9% spontaneous cases, 11.9% non-interventional/post marketing cases, and 0.02% literature) for the topic use of COVID-19 VACCINE ASTRAZENECA with seasonal influenza vaccine.

Of the 10841 cases, 74.9% were reported in females, 22.6% were reported in males. Gender was not reported in the remaining 2.5% of cases. The age ranged from 18 years to <65 years in 71.6% of the reports, 65+ years in 22.4%, and 0.43% in less than 18 years of age. In 5.5% cases the age was reported as Unknown. 99.9% of reports were medically confirmed reports, with remaining 0.1% being not medically confirmed (consumer reports).

Of the 10841 reports, 68.5% (7420) were serious, and 31.5% (3421) were non-serious. Outcome of fatal was reported in 32 (0.3%) of the total case count.

The information on days to onset of event from the time of receiving COVID-19 VACCINE was available in 8263 of the 10841 reports. 35.0% of events occurred within day 0 of vaccination, 26.5% occurred on day 1 post vaccination, 9.0% events occurred within day 2-15 post-vaccination, 1.9% events occurred between 16-200 days post-vaccination, 0.4% events occurred <200 days post-vaccination, 27% events where the number of days to onset was not reported.

Outcome was reported in 86.3% of the events, with 42.5% reported as recovered, 20.9% as recovering, 1.2% as recovering with sequelae, 21.4% not recovered. Outcome was unknown/not provided in 13.6% of the events. The top 20 reported PTs are headache (5555), pyrexia (3936), fatigue (3738), chills (3441), nausea (2832), myalgia (1997), arthralgia

(1532), pain in extremity (1345), dizziness (1291), pain (902), malaise (890), tremor (736), influenza like illness (713), vomiting (660), hyperhidrosis (562), Diarrhoea (532), decreased appetite (465), influenza (438), paraesthesia (433) and migraine (429).

Assessment for cases received with Herpes vaccine:

This search identified 1 spontaneous case received via health authority for the topic use of COVID-19 VACCINE ASTRAZENECA with Herpes vaccine. This serious case was reported in a PPD patient of PPD years of age, who experienced the events TCP, PE, COVID-19 pneumonia, sickle cell anaemia with crisis, chest pain, lung opacity, atelectasis, and oxygen saturation decreased.

The time to onset of the events from the time of receiving COVID-19 VACCINE was reported to be 17 days for sickle cell crisis, 22 days for PE, and oxygen saturation decreased. The time to onset for 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.

Assessment for cases received with Pneumococcal vaccine:

This search identified a total of 225 cases (87.1% spontaneous cases, and 12.9% non-interventional/post marketing cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Pneumococcal vaccine.

Of the 225 cases, 72.0% were reported in females, 25.3% were reported in males. Gender was not reported in the remaining 2.7% of cases. The age ranged from 18 years to <65 years in 50.7% of the reports, 65+ years in 43.6%, and 1.3% in less than 18 years of age. In 4.5% cases the age was not reported. 100% of reports were medically confirmed reports received from the regulatory authority.

Of the 225 reports, 71.6% (161) were serious, and 28.4% (64) were non-serious.

The information on days to onset of event from the time of receiving COVID-19 VACCINE was available in 789 (67.7%) of the 1165 events reported. 37.1% of events occurred within day 0 of vaccination, 21.0% occurred on day 1 post vaccination, 8.2% events occurred within day 2-15 post-vaccination, 1.5% events occurred between 16-100 days post-vaccination. 32.3% events where the number of days to onset post vaccination was not reported.

Outcome was reported in was reported in 83.1% of the events, with 42.7% reported as recovered, 17.7% as recovering, 1.3% as recovering with sequelae, 21.4% not recovered. Outcome was unknown/not provided in 16.9% of the events. The top 20 reported PTs are

headache (109), pyrexia (78), fatigue (78), chills (70), nausea (49), myalgia (41), pain in extremity (36), arthralgia (33), dizziness (31), malaise (23), pain (18), tremor (18), feeling cold (15), hyperhidrosis (14), influenza like illness (14), asthenia (13), back pain (12), chest discomfort (10), oropharyngeal pain (10), and vomiting (10).

Assessment for cases received with Varicella vaccine:

This search identified a total of 28 cases (92.9% spontaneous cases, and 7.1% non-interventional/post marketing cases) for the topic use of COVID-19 VACCINE ASTRAZENECA with Varicella vaccine.

Of the 28 cases, 64.3% were reported in females, 28.6% were reported in males. Gender was not reported in the remaining 7.1% of cases. The age ranged from 18 years to <65 years in 21.4% of the reports, and 65+ years in 71.4%. In 7.1% cases the age was not reported. 100% of reports were medically confirmed received from the regulatory authority.

Of the 28 reports, 60.7% (17) were serious, and 39.3% (11) were non-serious.

The information on days to onset of event from the time of receiving COVID-19 VACCINE was available in 70 (52.2%) of the 134 events reported. 23.1% of events occurred within day 0 of vaccination, 15.7% occurred on day 1 post vaccination, 9.7% events occurred within day 2-15 post-vaccination, 3.7% events occurred between 16-100 days post-vaccination. 47.8% events where the number of days to onset post vaccination was not reported.

Outcome was reported in was reported in 82.8% of the events, with 38.8% reported as recovered, 24.6% as recovering, 3.7% as recovered with sequelae, 15.7% not recovered. Outcome was unknown/not provided in 17.2% of the events. The top 20 reported PTs are pyrexia (11), nausea (8), headache (8), fatigue (7), chills (5), arthralgia (4), vertigo (4), myalgia (4), pain in extremity (3), dizziness (3), palpitations (2), influenza like illness (2), back pain (2), malaise (2), asthenia (2), urticaria (2), syncope (2), abdominal pain upper (2), herpes zoster (2), and dreamy state (2).

Conclusion

From the data identified 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 and included in the Core and EU RMPs.

Use 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. Refer to Appendix 4 for additional details.

Additional information regarding the Use of COVID-19 VACCINE ASTRAZENECA with other vaccines 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 RMP, Version no. 3, dated 28 April 2021) and EU RMP (Version 3.0, Succession 2; Internal Approval Date: 27 May 2021) included the following important identified and important potential risks, and missing information characterised in Sections 16.4.1, 16.4.2 and 16.4.3 respectively.

16.4.1 Important Identified Risks

The following safety concern is considered as important identified risks for COVID-19 VACCINE ASTRAZENECA:

- Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome (Section 16.4.1.1).

16.4.1.1 Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Table 53 Important Identified Risk: Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Characterisation	Summary
Frequency	• Post-market: Cumulative search until 28 June 2021 resulted in a total of 1375 individual cases of thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome. Clinical-trials: There were no reports of Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome in the COVID-19 VACCINE ASTRAZENECA clinical development programme.
Potential mechanism	The exact mechanism of thrombosis with thrombocytopenia following immunisation with COVID-19 VACCINE ASTRAZENECA is unknown. Several hypothetical biological mechanisms (eg, vaccine induction of PF-4 autoantibodies) have been proposed to explain the pathophysiology of thromboembolic events with TCP following vaccination (Greinacher A et al 2021);

Table 53 Important Identified Risk: Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Characterisation	Summary
	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 in combination with thrombocytopenia in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the CDS, HCPs should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal 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 recognized or managed appropriately and 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 of these events.

CDS Core Data Sheet, COVID-19 Coronavirus Disease 2019, HCP Healthcare Professionals, PF-4 Platelet Factor -4.

16.4.2 Important Potential Risks

The following two 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/Vaccine-associated enhanced respiratory disease (Section 16.4.2.2).

16.4.2.1 Important Potential Risks: Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Table 54 Important Potential Risk: Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Characterisation	Summary
Frequency	• Post-market: Cumulative search until 28 June 2021 resulted in a total of 3525 individual cases within the concept of Immune-mediated neurological disorders. The most commonly reported PTs were: Neuralgia (1524), Guillain-Barre syndrome (608), Sensory disturbance (336), Sensory loss (291), Neuropathy peripheral (263), Myelitis transverse (86), Multiple sclerosis (84), Optic neuritis (73), Multiple sclerosis relapse (60), Encephalitis (72), Demyelination (41), Polyneuropathy (40), Myelitis (35), Neuritis (27), Miller-Fisher syndrome (26), Acute disseminated encephalomyelitis (25) and Encephalopathy (21). • Clinical-trials: A review of the events in the pooled safety dataset in the MedDRA System Organ Class (SOC) of Nervous System Disorders in COVID-19 VACCINE ASTRAZENECA-treated participants (any dose group) demonstrated that reactogenicity ADRs comprised the majority of events in this SOC. No imbalance (between the COVID-19 VACCINE ASTRAZENECA group and the control group) in the incidence of events in the Nervous System Disorders SOC were noted when reactogenicity ADRs were removed. • Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the USA study, neurologic or neuroinflammatory AESIs were reported in 0.6% (121/21,587 participants) in the COVID-19 VACCINE ASTRAZENECA 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 COVID-19

Table 54 Important Potential Risk: Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Characterisation	Summary
	VACCINE ASTRAZENECA 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 participants (0.1%) in the COVID-19 VACCINE ASTRAZENECA 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 nonserious AEs of facial paralysis, occurring in 4 participants in the COVID-19 VACCINE. ASTRAZENECA group and 3 participants in the control group. In the US study, there were 5 nonserious AEs of facial paralysis, all in the COVID-19 VACCINE ASTRAZENECA group. In the USA study, there was 1 SAE of a demyelinating event: a participant in the COVID-19 VACCINE ASTRAZENECA 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 COVID-19 VACCINE ASTRAZENECA 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 biological mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of immunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton KR et al 1994).
Risk groups or risk factors	There are no known risk factors for the development of nervous system disorders, including immune-

Table 54 Important Potential Risk: Immune-mediated neurological conditions/Nervous system disorders, including immune-mediated neurological conditions

Characterisation	Summary
	mediated neurological conditions, following vaccination.
Preventability	Prevention of nervous system disorders, including immune-mediated neurological conditions, in the context of SARS-CoV-2 vaccination is unknown.
Impact on the risk-benefit balance of the product	Severe neurological conditions, if not recognized or managed appropriately, may result in persistent or significant disability or incapacity.
Public health impact	Severe neurological disorders are very rare, and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

ADRs Adverse Drug Reaction, AEs Adverse Events, AESIs Adverse Event of Special Interest, PTs Preferred Terms, MedDRA Medical Dictionary For Regulatory Activities, SAE Serious Adverse Event, SOC System Organ Class, SARS-CoV-2 Severe Acute Respiratory Coronavirus 2, USA United States of America.

16.4.2.2 Important Potential Risk: Vaccine-associated enhanced disease (VAED)/Vaccine-associated enhanced respiratory disease (VAERD)

Table 55 Important Potential Risk: Vaccine-associated enhanced disease (VAED)/Vaccine-associated enhanced respiratory disease (VAERD)

Characterisation	Summary
Frequency	• Post-market: Cumulative search until 28 June 2021 resulted in a total of 882 individual cases of potential VAED/VAERD. There have been no confirmed post-marketing reports of VAED/VAERD. • Clinical-trials: In the COVID-19 VACCINE ASTRAZENECA clinical programme, there was no evidence of an association between COVID-19 VACCINE ASTRAZENECA and VAED/VAERD. Proportionally more AESIs based on study specific lists of terms related to COVID-19 occurred in the control group than among COVID-19 VACCINE ASTRAZENECA recipients. In the USA study, COVID-19 related AESIs were reported in 1.7% (374/21587 participants) of the COVID-19 VACCINE ASTRAZENECA group and in 3.4% (362/10792 participants) of the placebo

Table 55 Important Potential Risk: Vaccine-associated enhanced disease (VAED)/Vaccine-associated enhanced respiratory disease (VAERD)

Characterisation	Summary
	group. In the pooled Oxford studies as of 07 December 2020, COVID-related AESIs were reported in 0.1% (15/12282 participants) of the COVID-19 VACCINE ASTRAZENECA group and 0.3% (36/11963 participants)of the control group.
Potential mechanism	The pathogenesis of VAED in the context of SARS-CoV-2 infection is unclear and there are no consistent mechanisms or immune markers of disease enhancement from non-clinical studies (Haynes BF 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 tract or may be part of a systemic process.
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 infection is currently unknown.
Impact on the risk-benefit balance of the product	VAED/VAERD may present as a 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. Patients diagnosed with ARDS have poorer prognosis and potentially higher mortality rates.
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, COVID-19 Coronavirus Disease 2019, SARS-CoV-2 Severe Acute Respiratory Coronavirus 2, USA United States of America, VAED Vaccine-Associated Enhanced Disease.

16.4.3 Missing information

The following 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 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 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. Whilst preliminary no-clinical safety studies have not indicated any concern to date, the effect of COVID-19 VACCINE ASTRAZENECA on the foetus and breastfed infant is unknown, as data are currently insufficient to inform on any vaccine-associated risk. Use of COVID-19 VACCINE ASTRAZENECA during Pregnancy and Neonatal outcome is considered and AESI for COVID-19 VACCINE ASTRAZENECA and reviews of these topics have been provided in each COVID-19 VACCINE ASTRAZENECA Monthly Summary Safety Report (MSSR) submitted globally and included in Section 16.3.5.1 of this PBRER. To date, from the data identified during the monthly reporting periods and also from the cumulative experience, 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.

A review of the pregnancy exposure reports did not reveal any new or unexpected trends or safety concerns. Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women will be investigating 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, an 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 would be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Use in immunocompromised patients will be investigated in the planned PASS activities (EAS, a post-marketing observational study using existing secondary health data sources in

patients receiving immunosuppressant medication or with primary immunodeficiency, and an interventional study in immunocompromised adults), and in going study 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)

Frail subjects with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) 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 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.

Use in frail patients with co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) 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 (eg, seasonal illness vaccines [such as the influenza and pneumococcal vaccines]) has not been evaluated. Therefore, while there is currently no evidence to suggest these safety profile of the subjects receiving COVID-19 VACCINE ASTRAZENECAL when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

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 studies using existing secondary health data sources). Vaccines to be evaluated include the influenza and pneumococcal vaccines.

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

At the beginning of the reporting period, COVID-19 VACCINE ASTRAZENECA was approved for "active immunisation of individuals ≥ 18 years old for the prevention of COVID-19".

SARS-COV-2 is a respiratory virus spreading easily through droplets from human to human. WHO declared a global pandemic in March 2020. As of August 2021 over 4 million people had died worldwide 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.

COVID-19 VACCINE ASTRAZENECA vaccine efficacy reported in Section 7 was demonstrated in randomised double blind control trials that included either saline solution or meningococci vaccine as comparator groups.

Data obtained from pooled data analyses of Oxford Clinical trials and from a large USA clinical trial indicated COVID-19 VACCINE ASTRAZENECA was able to protect older adults and patients with co-morbidities against hospitalization and death.

A summary of new information supporting the efficacy and effectiveness of COVID-19 VACCINE ASTRAZENECA against COVID-19 is provided below.

The efficacy of a two-dose regimen of COVID-19 VACCINE ASTRAZENECA has been currently investigated in 6 ongoing clinical trials (pooled COV001 (UK), COV002 (UK), COV003(Brazil), COV005 (South Africa) and in a separate large trial conducted in USA, Peru and Chile.

A prespecified pooled analysis of Phase III trials of COVID-19 VACCINE ASTRAZENECA for the prevention of symptomatic disease caused by SARS-CoV-2 was reported (Studies registered as ISRCTN89951424, NCT04324606, NCT04400838 and NCT04444674). The data cut-off for these analyses was 07 December 2020 (DCO2). Individuals 18 years of age and older were randomised 1:1 to receive two standard doses (SD) of COVID-19 VACCINE ASTRAZENECA or a control vaccine/saline placebo.

17.1 Newly identified information on efficacy/effectiveness

New information for the reporting period is from a Phase III, double-blind, randomised, placebo controlled trial for the efficacy, safety, and immunogenicity of COVID-19 VACCINE

ASTRAZENECA which is ongoing in adults 18 years and older in USA, Chile, and Peru for which a pre-specified interim analysis was announced on 22 March 2021.

At the data cut-off of 05 March 2021, the primary efficacy analysis included the accrual of 190 symptomatic cases of COVID-19 from the 26406 study participants who were seronegative at baseline, received 2 doses of study intervention (4 weeks apart), and were followed for ≥ 15 days post second dose without having a prior SARS-CoV-2 RT-PCR confirmed infection.

The primary endpoint of VE at preventing symptomatic COVID-19 illness was 76.0% (95% CI: 67.6%, 82.2%). An updated primary efficacy analysis included the accrual of 203 symptomatic cases of COVID-19 from the 26212 study participants who were seronegative at baseline, received 2 doses of study intervention (4 weeks apart), and were followed for ≥ 15 days post second dose without having a prior SARS-CoV-2 RT-PCR confirmed infection. The updated primary endpoint of VE at preventing symptomatic COVID-19 illness was 74.0% (95% CI: 65.3%, 80.5%). In addition, results were comparable across age groups, with VE of 72.8% (95% CI: 63.4%, 79.9%) in adults ≥ 18 to < 65 years and 83.5% (95% CI: 54.2%, 94.1%) in adults ≥ 65 years of age. A key secondary endpoint, preventing severe or critical disease, demonstrated 100% efficacy. There were 8 cases of severe COVID-19 in the primary analysis with all of those cases occurring in the placebo group. Vaccination with COVID-19 VACCINE ASTRAZENECA was well tolerated in this study. The incidence of SAEs was low (< 1%) in both the COVID-19 VACCINE ASTRAZENECA and placebo groups, with no difference in either frequency or type of SAEs between the treatment groups. No death was considered related to COVID-19 VACCINE ASTRAZENECA by the investigator.

The results from this primary analysis of the Phase III trial of COVID-19 VACCINE ASTRAZENECA in the USA have confirmed VE consistent with the pooled analysis of studies COV001, COV002, COV003, and COV005.

In addition, new information on COVID-19 VACCINE ASTRAZENECA immunogenicity was also available from USA clinical trial. The humoral immunogenicity of COVID-19 VACCINE ASTRAZENECA in Pivotal Study D8110C00001 for the overall immunogenicity analysis set was determined using validated bioanalytical methods to assess S-binding and pseudo neutralising antibodies. Overall, COVID-19 VACCINE ASTRAZENECA generated a robust humoral response, including when stratified by age, race, and with longer dose intervals. Spike-binding antibodies were detected 14 days after a first dose of COVID-19 VACCINE ASTRAZENECA (median 1988 AU/mL) and further increased after a second dose, peaking 14 days after a second dose (median 25509 AU/mL). Anti-S responses were maintained through at least Day 90, dropping off minimally from the peak responses induced at Day 43. Neutralising antibody responses had similar kinetics of induction, although median

titers were not raised over baseline at Day 15 due to a lower sensitivity associated with the pseudo neutralisation assay as compared to the S-binding antibody assay.

Furthermore, real world studies have demonstrated that 1 dose of COVID-19 VACCINE ASTRAZENECA resulted in substantial reductions in the risk of COVID-19-related hospitalisation in elderly, frail patients (≥ 80 years of age) with extensive comorbidities in the UK (Hyams C et al 2021). Similarly, Bernal and colleagues reported that vaccination with a single dose of COVID-19 VACCINE ASTRAZENECA was associated with a significant reduction in symptomatic SARS-CoV-2-positive cases in older adults (age ≥ 70 years) in England, with even greater protection against severe disease and sustained protection for the duration of follow-up (> 6 weeks) (Bernal et al 2021). In another real world setting populational study, 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). More recently, a cohort study (VIVALDI) comparing vaccinated and unvaccinated long-term care facility residents (N = 10412) aged ≥ 65 found that a single dose of COVID-19 VACCINE was able to prevent infection with SARS-COV-2 between 4-7 weeks after vaccination (Shroti et al 2021. Together, data from these real-world studies support the effectiveness of COVID-19 VACCINE ASTRAZENECA in protecting against SARS-CoV-2 infection in various populations.

17.1.1 Newly identified information on Efficacy of COVID-19 VACCINE ASTRAZENECA Against SARS-CoV-2 Variants.

New variants of SARS-CoV-2 have arisen that may maintain or increase virulence of the virus and increase transmissibility. Over 900 SARS-CoV-2 lineages have now been identified globally and as vaccination and natural infection increase immune pressure against the virus, novel SARS-CoV-2 variants of concern will continue to emerge. A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of SARS-CoV-2 variants, specifically B.1.1.7 (alpha) in the UK, B.1.351 (beta) in South Africa, and P.1 (gamma) in Brazil. These variants carry mutations in the S protein sequence: 9 in B.1.1.7, 10 in B.1.351, and 12 in P.1 compared with the Wuhan sequence (Boehm et al 2021).

These variants with extensive mutations in the RBD and N-terminal domain of the S protein are not just antigenically different but may also affect the transmission rate, disease severity, and efficacy of existing vaccines, thus impacting future development of vaccines and other therapies against COVID-19 (Volz et al 2021, Davies et al 2021, Pearson et al 2021, Wang et al 2021a, Muik et al 2021, Wu et al 2021, Madhi et al 2021).

Notable variants include B.1.351 first identified in South Africa in October 2020 and B.1.1.7 first identified in the UK in September 2020. A key issue is whether COVID-19 vaccines will be able to protect against infection or disease from the emerging new SARS-CoV-2 variants.

Evidence suggest that COVID-19 VACCINE ASTRAZENECA may have diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 (beta) variant which is also antigenically the most different from the Wuhan virus (Madhi et al 2021). The same level of resistance was not observed against the gamma (p1) variant, with COVID-19 VACCINE ASTRAZENECA yielding neutralising antibodies against the gamma variant in convalescent sera, albeit with reduced neutralisation level (Dejnirattisai W et al 2021).

Recently published reports on the efficacy of COVID-19 VACCINE ASTRAZENECA against the B.1.351, B.1.1.7 and B.1.617.2 variants are summarised below.

B.1.351 variant: An interim analysis of Study COV005 (South Africa) in participants aged 18 to 64 years (median 31 years) showed limited VE of 21.9% against mild to moderate disease (Madhi et al 2021). The majority of the COVID-19 cases (92.9%) in this study were due to B.1.351 variant and COVID-19 VACCINE ASTRAZENECA showed lower efficacy (10.4%) among these vaccinees. No determination of protection against severe disease or hospitalisation could be made since no events in these categories were reported. While the vaccine lacked efficacy against the B.1.351 variant, it was still demonstrated to have good efficacy (75.4%) against the predominant strain > 14 days after a single dose of COVID-19 VACCINE ASTRAZENECA prior to the emergence of the B.1.351 variant in South Africa.

B.1.1.7 variant (Alpha): A post-hoc analysis of the efficacy of COVID-19 VACCINE ASTRAZENECA against the B.1.1.7variant in Study COV002 (UK) showed that while laboratory nAb titres generated by vaccination with COVID-19 VACCINE ASTRAZENECA were lower for the B.1.1.7 lineage, clinical VE against symptomatic COVID-19 was observed for B.1.1.7 variant at 70.4%, with a lower bound of 43.6% for the 95% CI (Emary et al 2021).

A new variant of concern, B.1.617.2 (delta), initially identified in India in May 2021, has become dominant in the UK. A recent linkage healthcare data set study conducted in the UK, reported COVID-19 VACCINE ASTRAZENECA yielded vaccine effectiveness against hospitalisation of 71% of vaccinees after a single dose and 92% after 2 doses among over 14,000 patients who tested positive with the B.1.617.2 variant, indicating that COVID-19 VACCINE ASTRAZENECA remains effective against the most prevalent emergent variant dominant in the UK (Stowe J.et al).

17.2 Characterization of Benefits

The benefits of COVID-19 VACCINE ASTRAZENECA to prevent COVID-19 have been clearly demonstrated in randomised control trials and in the real world setting. 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 rates after a second dose. In particular, COVID-19 VACCINE ASTRAZENECA has the ability to elicit strong immune response and protection against hospitalisation of older adults with pre-existent comorbidities such as hypertension and Diabetes Mellitus, vulnerable populations at greater risk to die from COVID-19.

The updated evaluation of the efficacy of COVID-19 VACCINE ASTRAZENECA for prevention of COVID-19 is based on the pooled data from 4 ongoing clinical studies comprising adults aged from 18 up to 88 years (DCO2 data). There was good representation of persons at high risk of severe outcomes of COVID-19, including older adults (8% of participants were ≥ 65 years), and those with pre-existing comorbidities (36% of participants reporting cardiovascular disease, respiratory disease, diabetes, or obesity). However, individuals with severe or uncontrolled disease were excluded from the clinical studies. The updated primary efficacy analysis demonstrated effective protection of COVID-19 VACCINE ASTRAZENECA against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving two doses (SDSD or LDSD). Sensitivity analyses restricted to participants in the ITT analysis set also showed consistent vaccine efficacy.

DCO2 data consistently 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 (0 vs 14 cases in Control group, two of which were severe, including one with a fatal outcome).

Furthermore, COVID-19 VACCINE ASTRAZENECA vaccine efficacy was similar in participants with pre-existing comorbidity (vaccine efficacy = 62.71%, 95% CI: 44.79%, 74.82%), as compared with the overall population from 15 days after the second dose (SDSD + LDSD) in seronegative participants. Thus, the protection offered by COVID-19 VACCINE ASTRAZENECA against COVID-19 to those at greatest risk of severe outcomes of COVID-19 is similar to that in the general population.

While the number of older adults (≥ 65 years) with available data in this updated dataset was too small to allow a precise determination of vaccine efficacy, COVID-19 VACCINE ASTRAZENECA appeared to be as efficacious in this subgroup as in the general population, especially when post dose 1 efficacy was examined; these results were consistent between the interim and primary efficacy analyses. Reassuringly in this subgroup of older adults, the rates of seroconversion to binding and live neutralising antibody titres were similar to younger adults when examined within the same dose interval.

The interim and primary pooled efficacy analyses are based on limited duration of follow-up so to assess the duration of protection by COVID-19 VACCINE ASTRAZENECA against COVID-19, protection over longer follow-up time will be evaluated as more data from the ongoing studies accrue.

Overall, the updated analyses presented in this submission continue to provide robust support for the positive benefit-risk of COVID-19 VACCINE ASTRAZENECA use to protect against COVID-19 disease.

In the pooled studies, interpretation of VE estimates for individuals ≥ 65 years of age was limited by small numbers both of participants and of cases. However, study D8110C0001 includes a substantial subpopulation in this category, and the updated primary efficacy analysis provides strong evidence of vaccine efficacy in older adults (83.5%, [54.17, 94.06]). In addition, Study D8110C0001 demonstrated a higher VE point estimate among those with co-morbidities relative to the pooled studies (75.2% vs 62.7%, respectively). Taken together, these data demonstrate the continued efficacy of COVID-19 VACCINE ASTRAZENECA with the approved dosing approach despite differences in regions, rates of infection, and presence of local variants.

More recently, it has been shown that COVID-19 VACCINE ASTRAZENECA was able to retain efficacy against at least two out of the many variants of concern, yielding vaccine effectiveness of 92% against hospitalisation of people infected with the B.1.617.2 (delta) variant and 70.4% against symptomatic infection with the B.1.1.7 SARS-COV-2 variant indicating that COVID-19 VACCINE ASTRAZENECA remains effective against the most prevalent emergent variant dominant in the UK (Stowe J.et al).

Finally, COVID-19 VACCINE ASTRAZENECA offers flexible approach to dosing interval . 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.

Moreover, COVID-19 VACCINE ASTRAZENECA can be stored at 2°C to 8°C, facilitating distribution and allowing storage in domestic refrigerators for several months, which may allow access in healthcare settings, including care homes and pharmacies.

In summary, for the approved indication and over different age groups and regions, including Japan, the strength of evidence regarding efficacy is based on robust results from appropriate and generally accepted outcomes of controlled clinical trials demonstrating consistent results for clinically relevant endpoints.

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

A description of the medical need for COVID-19 VACCINE ASTRAZENECA and important alternatives available is provided for each of the approved indications 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.

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 and in more recently in the USA trial (D8110C00001) confirmed preliminary findings of good efficacy in older adults.

Important alternatives available

In December 2020, the first COVID-19 vaccine candidate (COVID-19 mRNA Vaccine BNT162b2) was granted in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 16 years of age. In January and March 2021, respectively, COVID-19 Vaccine Moderna and COVID-19 Vaccine Janssen 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. As of 15 February 2021, at least 7 different vaccines (utilising 3 platforms) have been administered globally (WHO 2021d). There are also approximately an additional 100 candidate vaccines in clinical development and approximately 184 are in nonclinical investigation.

18.2 Benefit-risk analysis evaluation

An evaluation of the benefit-risk profile for the use of COVID-19 VACCINE ASTRAZENECA in the approved 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

Demographics of the population in the proposed indication and risk factors for the disease:

WHO categorises COVID-19 disease severity as mild, moderate, clinical deterioration and critical illness. Global efforts to contain the epidemic aim to avoid the most severe forms of disease that result in hospitalisation and death, particularly amongst the most vulnerable adults with certain comorbidities and/or older age groups.

Individuals of any age can acquire SARS-CoV-2 infection, although the risk of severe COVID-19 increases with age. Epidemiological studies suggest that acute COVID-19 occurs at a lower frequency in patients < 18 years old than in adults (Christophers B.et.al, Kim L.et.al), with a smaller percentage of children with COVID-19 requiring hospitalisation or ICU admission relative to adults (CDC 2020a, ECDC 2020). Patients with COVID-19 can

experience a wide range of symptoms from mild to critical illness (ECDC 2020). Older adults and persons with medical conditions, including cardiovascular disease, chronic kidney disease, obesity, diabetes, pulmonary disease, immunosuppression, and sickle cell disease, are at increased risk of severe or critical disease (Gallo Marin B.et al 2021). Increasing evidence of disaggregated data from China and Europe suggest that the number of confirmed COVID-19 cases is comparable among men and women; however, men may have more severe illness and higher mortality from COVID-19 than women (Gebhard C.et al). In the USA, non-Hispanic American Indian, Alaska Native, and Black and Hispanic persons have been disproportionally affected (CDC 2021).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Estimated rates of asymptomatic SARS-CoV-2 infection are approximately 40% to 45%, with viral transmission possible from asymptomatic individuals (Lavezzo et al 2020,Oran and Topol 2020). Symptomatic patients can experience a range of symptoms from mild to critical illness. Based on the largest cohort study to date of >44000 persons with confirmed COVID-19 from China, the majority of patients experienced mild to moderate illness (Wu and McGoogan et al 2020):

- Mild (mild symptoms up to mild pneumonia): 81%.
- Severe (dyspnoea, hypoxia, or >50% lung involvement on imaging): 14% Critical (respiratory failure, shock, or multiorgan system dysfunction): 5% Overall, among patients who developed severe illness, the median time to dyspnoea ranged from 5 to 8 days, the median time to ARDS ranged from 8 to 12 days, and the median time to ICU admission ranged from 10 to 12 days (Huang et al 2020, Wang et al 2020, Yang et al 2020, Zhou et al 2020). Among all hospitalised patients, a range of 26% to 32% of patients were admitted to the ICU. Among all patients, a range of 3% to 17% developed ARDS compared to a range of 20% to 42% for hospitalised patients and 67%to 85% for patients admitted to the ICU. Mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study. The median length of hospitalisation among survivors was 10 to 13 days (Chen et al 2020, Guan et al 2020, Huang et al 2020, Wang et al 2020, Wu et al 2020a, Yang et al 2020).Complications associated with COVID-19.
- Acute respiratory distress syndrome is included in the most severe diseases category and is defined as the acute onset of hypoxaemia and bilateral pulmonary oedema caused by excessive alveolocapillary permeability. In earlier case series, up to 24% of hospitalised patients required mechanical ventilation (Petrilli et al 2020, Richardson et al 2020, Yang et al 2020).

- Arrhythmias, acute cardiac injury, cardiomyopathy, and shock (Arentz et al 2020, Cao et al 2020, Chen et al 2020, Wang et al 2020).

- Thromboembolic complications, including PE and acute stroke (Danzi et al 2020, Klok et al 2020, Mao et al 2020, Zhang et al 2020). Large vessel thromboembolisms have also been reported in patients < 50 years of age without risk factors (Oxley et al 2020).

- Laboratory evidence of an increased levels of proinflammatory cytokines, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (eg, Ddimer, ferritin), and elevated proinflammatory cytokines have been associated with critical and fatal illnesses (Huang et al 2020, Mehta et al 2020).

- Central and peripheral nervous system complications including GBS (Paterson et al 2020, Toscano et al 2020), encephalopathy (Helms et al 2020), meningo-encephalitis (Moriguchi et al 2020), ADEM (Paterson et al 2020), and acute necrotizing encephalopathy (Poyiadji N 2020).

    - Neurologic complications, in particular encephalopathy, manifesting with agitated delirium, was common in patients with critical illness.

    - Delirium/encephalopathy was reported in approximately two thirds of patients with COVID-19-related ARDS (Helms et al 2020).

    - A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has been described in children with COVID-19 (Licciardi et al 2020).

    - Secondary infections and bacterial or fungal coinfections were reported in 8% of patients (in 62 of 806); these included mainly respiratory infections and bacteraemia (Rawson et al 2020). Several reports of invasive pulmonary aspergillosis among immunocompetent patients with ARDS from COVID-19 have been described (Koehler et al 2020, Rutsaert et al 2020).

    - Psychotic symptoms have been related to other CoV infections. Structured delusions mixed with confusional features were the most frequent psychiatric manifestations observed in the COVID-19 patients. Psychotic symptoms were seen in patients with no previous history of psychosis (Parra et al 2020, Rogers et al 2020, Varatharaj et al 2020). According to the WHO, the average recovery time from COVID-19 is approximately 2 weeks for mild illness and 3 to 6 weeks for severe illness, with wide ranges dependent on risk factors and comorbidities (WHO 2021a).

18.2.1.2 Considerations relating to key benefit(s)

There remains an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Currently there are four vaccines approved in the EU to prevent COVID-19 disease.

World Health Organization provided an updated 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). 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. The benefits are clear 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 EU and Core RMP: Thrombosis in combination with thrombocytopenia and one additional important identified risk was included in the EU RMP: Anaphylaxis. Considerations regarding key risks are summarised below:

Thrombosis in combination with thrombocytopenia: This risk was added during the reporting period based on post-market data. CDS reflects AstraZeneca's position on this risk.

Nervous system disorders, including 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.

Anaphylaxis: The identified risk of anaphylaxis was based on a reasonable possibility of a causal association between COVID-19 VACCINE ASTRAZENECA treatment and anaphylaxis. Review of these events as of the cut-off of Addendum to Clinical Overview (ACO) has not indicated any change in frequency or severity.

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 ACO 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 two large studies which are randomised, controlled trials.

The study design and VE definitions used the WHO clinical progression scale (WHO et al 2020). 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.

Data on VE is available for approximately 11 weeks of follow-up since dose 2; therefore, the duration of protection and long-term safety are unknown until more information is available from follow up. 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, given the paucity of data, the possibility cannot be excluded. 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 in patients with immunisation to prevent COVID-19. 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 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 by SARS-CoV-2 in individuals 18 years of age and older.

Prior to the reporting period, VE was estimated from the previously pooled analysis of 4 studies (UK Phase I/II Study COV001, UK Phase II/III Study COV002, Brazil Phase III Study COV003, and South Africa COV005). 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.

During the reporting period, the COVID-19 VACCINE ASTRAZENECA CDS was updated to include Anaphylaxis and hypersensitivity with anaphylaxis (Sections 4.4 and 4.8), Thrombosis in combination with thrombocytopenia (Sections 4.3, 4.4 and 4.8) and TCP (Section 4.8).

In addition, global local labels, including the EU SmPC underwent further revisions to incorporate impositions including a contraindication for use in persons with a prior history of capillary leak syndrome, a warning and precaution about CLS and GBS with COVID-19 VACCINE ASTRAZENECA, and addition of CLS and TCP as ADRs.

There were no important identified risks prior to the reporting period. During the reporting period, the Core and EU RMPs were updated to include TTS. In addition, the EU RMP was updated to include Anaphylaxis as an Important Identified Risk and Thrombosis as an Important Potential Risk. Furthermore, AstraZeneca received an imposition from PRAC to include “Thrombocytopenia with associated bleeding” as an Important potential risk in the safety concerns of the EU RMP. This update was submitted to EMA on 12 August 2021.

Over 391 million doses of COVID-19 VACCINE ASTRAZENECA vaccines have been administered globally since 29 December 2021, with an additional 57,000 individuals receiving COVID-19 VACCINE ASTRAZENECA as part of the clinical development programme. From the clinical trial programme, 260 individuals <17 years, 47543 individuals 18 – 64 years of age, and an additional 9662 individuals >64 years of age have received at

least one dose of COVID-19 VACCINE ASTRAZENECA. From the post-marketing administration data available from the EU, UK, and Australia, a total of 10 million doses have been administered to individuals 18 – 49 years of age, 25.5 million doses have been administered to individuals 50 – 69 years of age, with 17.7 million doses administered to individuals 70 years of age and older. Cases of particular interest, including TTS, GBS, ADEM, encephalitis, and acute macular neuro-retinopathy have occurred across all age groups. In response to PRAC's request, observed vs. expected analyses have been expanded to include age and gender stratification for many of the topics of interest as exposure data becomes available. In instances where observed vs. expected analyses have trended toward a particular age group, medical review has not identified age as a factor of causality for the events of interest. Sources of reporting bias in voluntary systems, such as Yellow Card may be a factor.

Furthermore, an imbalance in adverse events for a particular age group has not been identified to date through the clinical trial programme, which provides more complete data for case assessment and is less prone to bias often encountered in the post-marketing environment. AstraZeneca maintains a robust surveillance programme for all adverse events occurring across all age groups. Any signals arising through these surveillance activities will be reported in future monthly summary reports and PBRERs.

The benefit of vaccination with COVID-19 VACCINE ASTRAZENECA has been weighted against the safety experience from the clinical programmes, as well as from post-marketing use. The data received during this reporting period 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 current benefit-risk profile for COVID-19 VACCINE ASTRAZENECA across all age groups.

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 R8 provide information meeting local requirements.

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