2.4. Nonclinical Overview

Drug Substance	AZD1222
ANGEL ID	Doc ID-004365565
Date	21 December 2020

2.4 Nonclinical Overview AZD1222

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

AstraZeneca (the Sponsor) is developing AZD1222 for the prevention of coronavirus disease-2019 (COVID-19). AZD1222 is a recombinant chimpanzee adenovirus (ChAd) expressing the severe respiratory syndrome-coronavirus-2 (SARS CoV-2) spike (S) surface glycoprotein. Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford with subsequent transfer of development activities to the Sponsor.

AZD1222 is a recombinant replication-defective ChAd vector expressing the SARS CoV-2 S surface glycoprotein, driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator (tPA) leader sequence at the N terminus. Spike (S) is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the SARS-CoV-2 virion. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 (ACE-2) binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S in receptor binding and membrane fusion make it a desirable target for vaccine and antiviral development. AZD1222 expresses a codon-optimised coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947.

The ChAdOx1 platform technology was used to support the first-in-human (FIH) and other early clinical AZD1222 studies. This approach of using platform data to support a FIH clinical study is consistent with the views expressed by global regulators at the International Coalition of Medicines Regulatory Authorities – Global Regulatory Workshop on COVID-19 vaccine development, 18 March 2020 (ICMRA 2020).

To date, immunology and biological activity studies (including prime boost vaccination) of AZD1222, have been conducted in mice, non-human primates, ferrets and pigs (Table 1).

For the FIH study, biodistribution studies with AZD1222 were not performed based upon previously generated biodistribution data with similar replication-defective ChAd vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice that showed no evidence of replication of the virus or presence of disseminated infection after intramuscular (IM) injections (Table 2). A recent biodistribution study (Table 2) of IM ChAdOx1 HBV in mice detected, based on interim data using a qPCR method, low levels of disseminated ChAdOx1 HBV. Low copy numbers were found in a range of organs (spleen, brain, heart, kidney, liver, lung, lymph node, testes, ovary) at levels 1,000 to 100,000 fold less than at the injection site (skeletal muscle). Toxicology studies on a related betacoronavirus (MERS-CoV) ChAdOx1 vectored vaccine expressing full-length S protein, as well as other ChAd vaccines (AdCh63 MSP-1, ChAd OX1 NP+M1) were also used to support the FIH study and are shown as a reference

(Table 2). Toxicology studies with AZD1222 have either been recently completed or are ongoing (Table 1 and Table 3). Ongoing or planned nonclinical studies are listed in Table 3.

All pivotal nonclinical safety studies were conducted in OECD member countries and in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP), and according to relevant International Conference on Harmonisation guidelines.

Table 1 List of Nonclinical Pharmacology Studies with AZD1222

Study (Report Number or publication)	Species	Dose and route of administration	Source	GLP Y/N
Primary Pharmacology				
Effect of D614G Mutation in SARS-CoV-2 Spike Protein on AZD1222 (20-01700)	In vitro	NA	CSIRO Health and Biosecurity, Australia	N
Murine Immunogenicity (van Doremalen et al 2020)	Balb/C and CD-1 mice	Single dose, IM 6×10^9 vp AZD1222	Jenner Institute - Oxford University, UK / NIH, USA	N
Murine Immunogenicity (Graham et al 2020)	Balb/C and CD-1 mice	Day 0 and 28 IM, 6.02 × 109 vp/animal AZD1222	Jenner Institute - Oxford University / Pirbright Institute, UK	N
Non-human Primate Efficacy and Immunogenicity (van Doremalen et al, 2020)	Rhesus macaques	Day 0 and 28, IM 2.5×10^{10} vp AZD1222 or ChAdOx1 GFP	Jenner Institute - Oxford University, UK / NIH, USA	N
Efficacy of ChAdOx1 nCoV-19 Against Coronavirus Infection in Rhesus Macaques (6284)	Rhesus macaques	Single dose, IM 2.5×10^{10} vp AZD1222	Jenner Institute - Oxford University / Public Health England, Porton Down, UK	N
Assessment of Efficacy of SARS-CoV-2Vaccine Candidates in the Ferret Mode (20-01125)	Ferret	Single dose, IM, IN 2.5×10^{10} vp AZD1222 or ChAdOx1 GFP	CSIRO Health and Biosecurity, Australia	N
Efficacy of ChAdOx1 nCoV-19 Against Coronavirus Infection in Ferrets (6285)	Ferret	Day 0 and 28, IM 2.5×10^{10} vp AZD1222 or ChAdOx1 GFP	Jenner Institute - Oxford University / Public Health England, Porton Down, UK	N

Table 1 List of Nonclinical Pharmacology Studies with AZD1222

Study (Report Number or publication)	Species	Dose and route of administration	Source	GLP Y/N
Porcine Immunogenicity (Graham et al 2020)	White-Landrace-Hampshire cross-bred pigs	Day 0 and 28, IM 5.12×10^{10} vp AZD1222	Jenner Institute - Oxford University / Pirbright Institute, UK	N
ChAdOxl-nCoV19 immunopotency assay (INT-ChadOx1 nCov19-POT004)	Balb/C and CD-1 mice	5×10^{9} vp AZD1222	Jenner Institute - Oxford University, UK	N
Safety Pharmacology				
Cardiovascular and Respiratory Assessment Following Intramuscular Administration to Male Mice (617078)	CD-1 mice	Day 4, IM 2.59×10^{10} vp AZD1222	Charles River Laboratories Ltd, UK	Y
Repeat Dose Toxicology				
AZD1222 (ChAdOx1-nCovd-19): A 6 Week Intermittent Dosing Intramuscular Vaccine Toxicity Study in the Mouse with a 4 Week Recovery (513351)	CD-1 mice	Days 1, 22 and 43, IM 3.7×10^{10} vp AZD1222	Charles River Laboratories Ltd, UK	Y
Developmental and Reproductive Toxicology				
ChAdOx1-nCovd19: A Preliminary Intramuscular Injection Vaccine Development and Reproductive Study in Female CD-1 Mice (490838)	CD-1 mice	Day 1 (13 days prior to pairing for mating) and GD 6 to EFD phase animals and on GD 6 and GD 15 to littering phase animals, IM 2.59×10^{10} vp AZD1222	Charles River Laboratories Ltd, UK	Y

CSIRO = Commonwealth Scientific and Industrial Research Organisation, Geelong, Australia; EFD = embryo-fetal development; GD = gestation day; IM = intramuscular; IN = intranasal; NIH = National Institute of Health

Table 2 List of Nonclinical Studies with Similar Replication-defective ChAd Vaccines (AdCh63 and ChAdOx1)

Study (Report Number)	Species	Dose and route of administration	Source	GLP Y/N
AdCh63 MSP-1 and MVA MSP-1 Tissue Distribution Study By Intra-Muscular Administration To Mice (Report UNO0014/RMBIODIST-001)	Balb/C mice	Day 1, IM 1.11×10^{10} vp AdCh63 MSP-1 1.04×10^{8} pfu MVA MSP-1	Huntingdon Life Sciences,[a] UK	Y[b]
AdCh63ME-TRAP Tissue Distribution Study By Intra-Dermal Administration To Mice (UNO0009/MAB-001)	Balb/C mice	Day 1, ID 3.3×10^{9} vp	Huntingdon Life Sciences,[a] UK	Y[b]
ChAdOx-1 HBV and MVA-HBV Biodistribution Study in BALB/c Mice with Shedding Assessment (0841MV38.001)	Balb/C mice	Days 1 and 28, IM 2.4×10^{10} vp ChAdOx-1-HBV 6.1×10^{7} pfu MVA-HBV	Calvert Laboratories, USA	Y
ChAdOx1 Chik Vaccine or ChAdOx1 MERS: Toxicity Study by Intramuscular Administration to Mice (QS18DL)	Balb/C mice	Day 1 and 15, IM 1×10^{10} vp	Envigo CRS Limited UK	Y
ChAd OX1 NP+M1 and MVA NP+M1: Toxicity Study by Intramuscular Administration to Mice (XMM0003)	Balb/C mice	Day 1, IM ChAd OX1 NP+M1 1×10^{10} vp and Day 15, IM MVA NP+M1 1.5×10^{7} pfu	Huntingdon Life Sciences,[a] UK	Y
Mouse Toxicity AdCh63 MSP-1 and MVA MSP-1 or a Combination of AdCh63 ME-TRAP and MVA ME-TRAP (UNO0013)	Balb/C mice	Day 1, IM AdCh63 MSP-1 1.11×10^{10} vp Day 15, IM MVA MSP -1 10.4×10^{7} pfu Day 1 and 15, IM AdCh63ME-TRAP/ MVA ME TRAP 0.78×10^{10} vp / 6.85×10^{7} pfu	Huntingdon Life Sciences,[a] UK	Y

[a] Currently Covance CRS Ltd.

[b] In-life phase conducted to GLP; biodistribution phase (RBIODIST-001 or MAB-001) not conducted to GLP

Table 3 List of Ongoing and Planned Nonclinical Studies with AZD1222

Study (Report Number)	Species	Status	GLP Y/N
AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse (514559)	CD-1 mice	Ongoing Audited draft February 2021	Y
AZD1222 (ChAdOx1 -nCovd19): An Intramuscular Vaccine Development and Reproductive Study in Female CD-1 Mice (490843)	CD-1 mice	Ongoing Audited draft February 2021	Y

2 PHARMACOLOGY

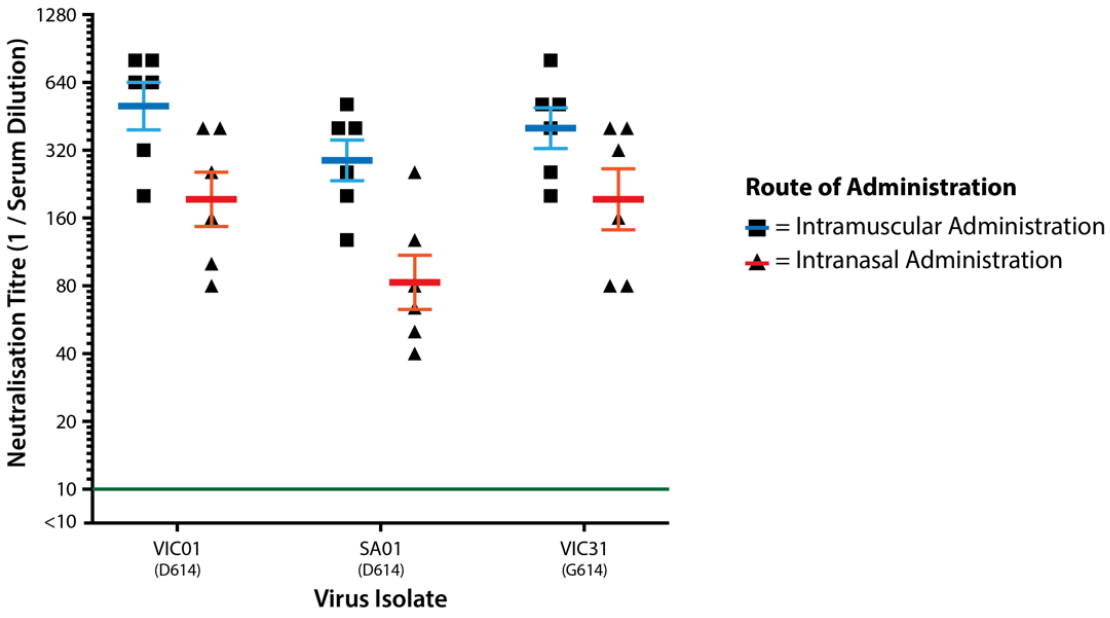
2.1 Primary Pharmacodynamics

Immunogenicity studies in animal models responsive to AZD1222 were conducted to evaluate the immunologic properties of this COVID-19 vaccine candidate to support FIH clinical trials. AZD1222 has been shown to be immunogenic in BALB/c, CD-1 mice, ferrets, non-human primate (NHP) and pig models. These studies included evaluation of humoral, cellular and functional immune responses. Whilst a single dose of AZD1222 induced antigen-specific antibody and T cell responses, a booster immunisation enhanced antibody responses, particularly in pigs, with significant increases in SARS-CoV-2 neutralising antibody titres (Graham et al 2020). A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated enhanced respiratory disease (ERD). A single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to vector controls (van Doremalen et al 2020). Importantly, no evidence of ERD following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed (van Doremalen et al 2020).

Mutations are occurring naturally within the SARS-CoV-2 genome. Most vaccines in development rely upon inducing immune responses towards Spike protein (S), the main virus surface protein. A D614G mutation in S is increasing in prevalence amongst sequenced viruses worldwide. The mutation is thought to increase infectivity of the virus by reducing S1 shedding, increasing infection (Zhang et al 2020). The effect of the D614G mutation on the efficacy of virus neutralisation following vaccination of ferrets with AZD1222 was assessed in study 20-01700 (Figure 1). A new Australian isolate containing the D614G mutation (VIC31) was obtained from VIDRL. Three isolates were used for virus neutralisation assays: SA01: has identical amino acid sequence in S to Wuhan-Hu-1. VIC01: S differs from SA01 by an Ser247Arg mutation. VIC31: S differs from SA01 by the Asp614Gly mutation.

Overall, there were no significant effects of the D614G mutation in the SARS-CoV-2 Spike protein on relative neutralisation of D614 and G614 variants with serum samples collected from ferrets that had received prime-boost administrations of AZD1222. Therefore, animal challenge studies presented are relevant to strains circulating in the human population.

Figure 1 Effect of D614G mutation on vaccine-induced antibody-mediated neutralisation.



Mean neutralising titres (calculated from log2-values) to three circulating Australian SARS-CoV-2 isolates. Neutralisation titres of serum samples collected following prime-boost vaccination with AZD1222 in ferrets, administered by two routes (intramuscular and intranasal). Bold horizontal lines represent overall mean titre of the vaccination route/isolate combination with uncertainty bars representing Standard Error of the Mean (SEM). Square and triangle marks represent mean titres of the triplicate titres for each serum sample/isolate combination.

Viral RNA in Gastrointestinal Tract

In the NHP pharmacology study (van Doremalen et al 2020), there was an unexpected finding of viral RNA in tissues of the gastrointestinal (GI) tract at 7 days post-challenge in immunised, but not control, animals. Viral gRNA load in intestinal tissues of prime-boost-vaccinated animals was higher than the levels measured in control and prime-only-vaccinated animals at 7 days post-challenge and was associated with the detection of sgRNA. However, no infection of intestinal tissue was observed by immunohistochemistry, nor were we able to detect infectious virus in intestinal tissue. Given that spike-specific antibodies were significantly increased after the second immunization (two-tailed signed-rank Wilcoxon test) higher viral gRNA load intestinal in prime-boost animals may correlate with

greater intestinal clearance and retention of opsonised virus following challenge. FcRn allows the entry and retrieval of IgG from the intestinal lumen throughout health and disease. This bidirectional transport allows the secretion of IgG into the lumen, the subsequent uptake of opsonized bacteria and viruses (Castro and Clatworthy 2020). As previously reported, SARS-CoV-2 antigen can be detected in lymphocytes and macrophages in the lamina propria of the intestinal tract of control animals (Munster et al 2020). This may indicate a higher proportion of plasma cells secreting IgA2 in the gut lamina propria of prime-boost-vaccinated animals and trapping of SARS-CoV-2 virus. Whilst SARS-CoV-2 virus may make its way to the gastric lumen, it would be subjected to the adverse effect of the acidic environment of the stomach that would significantly affects viability.

Nevertheless, SARS-CoV-2 can cause gastrointestinal symptoms, such as loss of appetite, vomiting, diarrhoea, or abdominal pain during the early phases of the disease (Villapol 2020). It has been reported in some patients that although SARS-CoV-2 has been cleared in the respiratory tract, the virus continues to replicate in the gastrointestinal tract and could be shed in faeces (Yang et al 2020). Currently, the exact mechanism of SARS-CoV-2 interaction with the gastrointestinal tract is still not fully understood. However, SARS-CoV-2 shows a high affinity to ACE2 receptors, making sites of high ACE2 receptor expression such as lungs and GI tract prime targets for infection (Dahiya et al 2020). It is therefore possible that gastrointestinal symptoms in COVID-19 are somehow caused by the direct attack of SARS-CoV-2 to gastrointestinal tract (Zhong et al 2020). If higher viral gRNA loads in intestinal tissues of prime-boost vaccinated animals is associated with continued replication then it was not associated with any signs of lesions or infection.

Lung Histopathology

In rhesus macaques 3 out of 6 control animals developed some degree of viral interstitial pneumonia following SARS-CoV-2 challenge. Lesions were widely separated and characterised by thickening of alveolar septum. Alveoli contained small numbers of pulmonary macrophages and rarely oedema. Type-II pneumocyte hyperplasia was observed. No histological lesions were observed in the lungs of vaccinees.

In comparison, the majority of histopathological findings made in the lungs of ferrets following SARS-CoV-2 challenge were modest at most. In control group 3a that received a prime with ChAdOx1 vector expressing green fluorescent protein (GFP) one ferret showed mild lesions compatible with acute bronchiolitis and the other animals were similar to group 1 primed with AZD1222. Only mild inflammatory cell foci and no lesions were observed in group 1. In group 2 that received a prime and boost with AZD1222, inflammatory cell were also detected in lungs. These changes are likely associated with an immune response to challenge as they were also observed in controls. In group 4 immunised with inactivated SARS CoV-2, mild to moderate lesions were observed in the lungs with inflammatory cells and perivascular cuffing at day 7 post challenge potentially indicative of enhanced respiratory

disease. In a second ferret study, no significant histological lung changes were present in any of the animals examined.

Enhanced respiratory disease (ERD) can result from immunization with antigen that is not processed in the cytoplasm, resulting in a nonprotective antibody response and CD4+ T helper priming in the absence of anti-viral cytotoxic T lymphocytes. This type of vaccine response can lead to a pathogenic Th2 memory response with eosinophil and immune complex deposition in the lungs after respiratory infection. For example, infants and toddlers immunized with a formalin-inactivated virus vaccine against respiratory syncytial virus (RSV) experienced an enhanced form of RSV disease characterized by high fever, wheezing and bronchopneumonia when they became infected with wild-type virus in the community (Acosta et al 2015). AZD1222 not expected to cause ERD because antigens are expressed intracellularly, generating anti-viral cytotoxic T cell and protective antibody responses.

In the van Doremalen et al study, significantly reduced viral load in the bronchoalveolar lavage fluid and lower respiratory tract tissue of vaccinated rhesus macaques challenged with SARS-CoV-2 with no pneumonia was observed compared to control animals. No evidence of immune-enhanced disease after viral challenge in vaccinated SARS-CoV-2-infected animals was found in terms of increased severity of viral infection. At present, there are no known clinical findings, immunological assays or biomarkers that can differentiate any severe viral infection from immune-enhanced disease, whether by measuring antibodies, T cells or intrinsic host responses (Arvin et al 2020). Carefully controlled human studies of sufficient size to enable the detection of increased frequency of severe cases in vaccinated cohorts compared to control group are required to determine if antiviral host responses may become harmful in humans.

In conclusion, the rhesus macaque is more predictive than ferret of histological lung changes and the ability of immunisation with AZD1222 to mitigate these following challenge with SAR-CoV-2. No enhanced respiratory disease was observed post challenge in AZD1222 immunised animals.

2.2 Secondary Pharmacodynamics

Secondary pharmacodynamic studies have not been conducted with AZD1222.

2.3 Safety Pharmacology

In a mouse cardiovascular and respiratory safety pharmacology study, a group of 8 male CD-1 mice were dosed by IM injection with the control item for AZD1222 (A438 buffer) on Day 1 and AZD1222 (2.59 x 10^{10} vp dose) on Day 4 (617078).

There were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters considered to be AZD1222-related. The No Observed Effect Level (NOEL) for cardiovascular and respiratory assessment was an AZD1222 dose of 2.59 x 10^{10} vp .

Irwin Screen observations (autonomic, neuromuscular, sensorimotor, behavioural parameters) and effects on body temperature and pupil size were made in the repeat-dose IM toxicity study (513351) in male and female CD-1 mice on Days 8 and 29 following administration of AZD1222 at 3.7 x 10^{10} vp on Days 1, 22. There were no effects on body temperature, pupil size or Irwin Screen observations considered to be AZD1222-related.The NOEL for the Irwin Screen phase was 3.7 x 10^{10}.

2.4 Pharmacodynamic Drug Interactions

Pharmacodynamic drug interaction studies have not been conducted with AZD1222.

3 PHARMACOKINETICS

3.1 Absorption

Absorption studies evaluations are not generally needed for vaccines. WHO guidelines on nonclinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune responses.

3.2 Distribution

Distribution studies are not generally needed for vaccines. WHO guidelines on nonclinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional ADME evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response.

Biodistribution studies are more informative when a replication-competent virus is administered since the amount of virus present in the subject (experimental animal or human volunteer) will increase following injection, and some viruses have a known propensity to accumulate in particular organs. For example, Vaccinia virus may be found at high titres in the ovaries and adenovirus accumulates in the liver. However, replication-deficient viruses are known to infect cells at the injection site, and although some infectious viral particles may drain to local lymph nodes and travel through the blood to other sites in the body, concentrations of virus at these sites are so low after dilution in the blood and other tissues that they are not reliably detected. A biodistribution study would demonstrate if, unexpectedly, viral replication was taking place after injection. However, this is not an

appropriate assay to use to detect replication competent virus, which is tested for in an in vitro assay which has much greater sensitivity for detecting even small amounts of replication competent virus in the vaccine preparation.

AZD1222 is replication-incompetent in human cells due to a block in gene expression caused by the deletion of the E1 genes. Therefore, after the initial infection of the cells that the virus enters, there will be no further infection and no spread of the virus within the body. Biodistribution studies with similar ChAd vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice have previously been performed and showed no evidence of replication of the virus or presence of disseminated infection after IM injection. A biodistribution and shedding study using the ChAdOx1 vector with an hepatitis B virus (HBV) insert after IM injection on Days 1 and 28 in mice was conducted (0841MV38.001). Distribution to some samples of all tissues was noted on day 2 and Day 29. The highest levels (copies/mg sample) were noted at the site of administration (skeletal muscle), ranging from 3×10^8 to 9.97×10^9 copies/mg sample. In the majority of samples of other tissues taken on Day 56, the levels were below the level of quantification, indicating elimination. Low levels were noted in 1 sample (of 6) for each of heart and liver, 1 of 3 for ovary and testes, and 3 of 6 lymph node samples at this timepoint. This study does not contain assessment of CNS, relevant peripheral nerves or bone marrow and it does not include analysis at shorter time points compared to the already available studies and no description of the validation of method analysis. This platform study will be superseded by a biodistribution study with AZD1222 (514559). This study includes additional early timepoints, an assessment of a full set of tissues including spinal cord and bone marrow. A draft report is due February 2021.

Intramuscular administration of AZD1222 is expected to minimise risk of systemic exposure. The biodistribution of AZD1222 following intramuscular administration is expected to be similar to that of AdCh63, confined to the site of injection and draining lymph nodes.

3.3 Metabolism

Metabolism studies have not been conducted with AZD1222. The expected consequence of metabolism of biotechnology-derived vaccines is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood.

3.4 Excretion

Excretion studies have not been conducted with AZD1222. No virus excretion is expected with AZD1222 as it is a non-replicating vaccine vector. Shedding of ChAdOx1 HBV in mice following IM administration of Days 1 and 28 have been assessed. DNA was extracted from mouse fecal and urine samples collected were all negative, suggesting that no shedding had occurred in these matrices at the times sampled.

3.5 Pharmacokinetic Drug Interactions

Pharmacokinetic drug interaction studies have not been conducted with AZD1222.

3.6 Other Pharmacokinetic Studies

Other pharmacokinetic studies have not been conducted with AZD1222.

4 TOXICOLOGY

4.1 SINGLE DOSE TOXICITY

No single dose toxicity studies have been performed with AZD1222.

4.2 REPEAT DOSE TOXICITY

A repeat-dose GLP toxicity study with AZD1222 in mice was initiated on the 9th September 2020, the audited draft results (excluding recovery pathology) are discussed below. A final report is due January 2021 (513351).

As the ChAdOx1 platform technology utilized for AZD1222 is well characterized, toxicology data with ChAdOx1 MERS-CoV vaccine expressing the full-length Spike protein in mice (Report QS18DL), was used to support first in human (FIH) clinical trials for AZD1222 (International Coalition of Medicines Regulatory Authorities – Global Regulatory Workshop on COVID-19 vaccine development, 18 March 2020 [ICMRA 2020]). In addition, toxicology studies on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) are also discussed.

4.2.1 A 6 -Week Intermittent Dosing Intramuscular AZD1222 Toxicity Study in Mice with a 4 Week Recovery

At the time of toxicology species selection only ChAdOx1 immunogenicity data for mouse and rhesus macaques was available to the sponsor. Pig and ferret immunogenicity data were subsequently made available. Considering the need to expedite toxicity testing given the urgency of the ongoing pandemic, the longer lead time for NHP toxicity studies and longer reproductive toxicity study requirements, the CD-1 mouse strain was selected as the toxicology species due to its larger size compared to the Balb/c mouse strain.

The objective of this study was to determine the potential toxicity of AZD1222 (total viral particle dose of $3.7x10^{10}$) when given by intramuscular injection intermittently (on Days 1, 22 and 43) to mice, with a 28 day recovery period to evaluate the potential reversibility of any findings (513351). In addition, the immunogenicity was evaluated. Scheduled necropsies were conducted either at the end of the 6 week treatment period (Day 45) or at the end of the 28 day recovery period.

The following parameters and end points were evaluated in this study: clinical signs, body temperature, body weights, body weight gains, food consumption, dermal scoring, Irwin screen observations, clinical pathology parameters (hematology and plasma chemistry), immunogenicity, gross necropsy findings, organ weights, and histopathological examinations.

In comparison to controls and pre-study data, a slightly higher body temperature was observed in AZD1222 treated males, notably on Days 22, 4 hours post dose (range 36.2-39.5ºC compared to 36.2-38.7ºC in controls) but was comparable to controls by 24 hours post-dose. There was no AZD1222-related change in body temperature recorded in males, as part of the Irwin observations.

In animals administered AZD1222, there was a mild decrease in monocytes on Day 45, which was consistent with expected pharmacology following immunisation. Additionally, globulin was mildly higher, and albumin and albumin/globulin ratio were minimally to mildly lower, which was consistent with an acute phase response. Following the recovery period, globulin remained mildly higher and albumin/globulin ratio remained mildly lower in AZD1222-treated females, the other changes had reversed.

All samples collected from animals during the pre-treatment phase prior to immunisation were below the limit of quantification (BLQ) for the assay (BLQ; 0.250 AU/mL) and considered seronegative. Samples collected indicate that all animals mounted an antibody response to S-glycoprotein following a single administration of AZD1222 on Day 1 with most animals showing a marked increase in the level of antibody response following a second administration of AZD1222 on Day 22. On Day 74, a further increase in antibody response or maintenance of response was observed in all animals following a third administration of AZD1222.

At histopathological examination of the main study animals, mononuclear and/or mixed cell inflammation was observed in the subcutaneous tissue and underlying skeletal muscle at the control and AZD1222 administration sites. This finding was of a higher incidence in animals dosed with AZD1222. In some animals there was an extension of the inflammatory cells into the fascia and connective tissue below the skeletal muscle at the administration sites, that extended to surround the sciatic nerve. The inflammatory cells did not extend into the endoneurium of the sciatic nerve and no findings were present in the underlying axons, which appeared histologically normal. Inflammatory cells were not observed in the nerve roots contained within the lumbar spinal cord sections, confirming that the epineurial/perineurial inflammatory cells noted in the sciatic nerve samples resulted from an extension of the inflammation from the adjacent injection site.

In conclusion, administration of AZD1222 to CD-1 mice (total viral particle dose of 3.7 x 10^{10}) by intramuscular injection on 3 occasions (once every 3 weeks) over a 43 day period was well tolerated, with a transiently higher body temperature in males, decreases in

monocytes in males and females (consistent with the expected pharmacology of AZD1222) and increase in globulin and decrease in albumin and albumin/globulin ratio, consistent with an acute phase response, observed.

In all animals dosed with AZD1222, antibodies against the S-glycoprotein were raised and maintained throughout the dosing and recovery periods in all animals.

In AZD1222 animals, higher spleen weights were observed but with no correlating macroscopic or microscopic changes. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with AZD1222 which were consistent with the anticipated findings after intra-muscular injection of vaccines.

4.2.2 Repeat-dose Toxicology Studies with Similar Replication-defective ChAd Vaccines (AdCh63 and ChAdOx1)

A brief summary of the key findings from the ChAdOx1 MERS vaccine toxicology study in in mice is provided below.

- Changes at the intramuscular injection sites (inflammatory cell infiltrates) were observed in the majority of females and in several males.
- Histopathological changes in the spleen (increased germinal center development) correlated with an increased spleen weight in females. Increased germinal center development of the right lumbar lymph nodes (draining lymph node), correlated macroscopically with enlargement, was observed for the majority of treated animals. Slightly higher circulating white blood cell numbers were observed.
- At the end of the study treatment there was a slightly lower than control body weight gain for treated males and females. For males this was due mainly to slightly lower than control weight gains during Days 15 to 18 however for females this was due mainly to small weight losses during this period. Mice were dosed on Day 1 and 15, with necropsy on day 28.
- Slightly lower group mean liver weight for males and females (0.92X and 0.90X control), higher phosphorus concentration for females (1.2X control) or lower triglyceride concentration for males and females (0.56X and 0.64X) were observed. There was no correlation with histopathological changes.

The spectrum and severity of these changes were consistent with the administration of an antigenic substance such as ChAdOx1 MERS, and were considered to be non-adverse.

Results from the toxicology studies on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) were consistent with ChAdOx1 MERS and were well tolerated with no associated adverse effects. The toxicity data (and toxicity in the target organs) from the ChAdOx1 and ChAd63 based vaccines follows the same pattern, where findings were consistent with a predicted response to vaccine administration.

4.3 Toxicokinetics

Toxicokinetic studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), Pharmacokinetic studies (eg, for determining serum or tissue concentrations of vaccine components) are normally not needed.

4.4 Genotoxicity (Mutagenicity)

Genotoxicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines, (WHO 2005), genotoxicity studies are normally not required for the final vaccine formulation and therefore have not been conducted.

4.5 Carcinogenicity

Carcinogenicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), Carcinogenicity studies are not required for vaccine antigens. AZD1222 is a replication deficient, non-integrating adenovirus vector so there is no risk of carcinogenicity. To date there have been no clinical reports of chromosomal vector integration following adenovirus vector-mediated gene transfer.

4.6 Developmental and Reproductive Toxicity

An evaluation of the impact of AZD1222 on embryo-foetal development was completed in a dose-range study (490838). The main GLP embryo-foetal development study is ongoing with an audited draft due end January 2021.

Intramuscular administration of AZD1222 to groups of CD-1 female mice on Day 1 (13 days prior to pairing for mating) and again on Gestation Day (GD) 6 at 2.59 x 10^{10} per occasion (embryofetal development phase), or on GD 6 and GD 15 at 2.59 x 10^{10} per occasion (littering phase) was well tolerated (490838). Anti-S glycoprotein antibody responses were raised in dams following administration of AZD1222 and these were maintained through the gestational and lactation periods. Seropositivity of fetuses and pups was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively. There were no AZD1222-related effects seen for dams in-life including at the injection site, for female reproduction, fetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no AZD1222-related fetal visceral or skeletal findings.

4.7 Local Tolerance

Local tolerance of AZD1222 was evaluated as part of the repeat dose toxicity study in mice (513351). There was no erythema or oedema at the injection sites after administration of

AZD1222 on any dosing occasion. Histopathology showed minimal subcutaneous oedema was observed in the administration sites in male and female animals from both the control group and those administered AZD1222 and was considered to be related to the route of administration. Minimal mononuclear or mixed cell inflammation was observed in the subcutaneous tissue and underlying skeletal muscle at the administration sites in both male and female animals. This finding was of a higher incidence in animals administered with AZD1222. In some animals there was an extension of the inflammatory cells into the fascia and connective tissue below the skeletal muscle at the administration sites. This resulted in inflammatory cells being noted surrounding the epineurium/perineurium of the sciatic nerve samples. In the hind limb, inflammation around the sciatic nerve due to local extension from the administration site is a well-recognized effect (Sellers et al 2020). Local tolerance was also evaluated as part of a repeat dose GLP toxicology study in mice with the related ChAdOx1 MERS vaccine (QS18DL). Changes related to treatment with ChAdOx1 MERS vaccine were seen in the tissues of the intramuscular injection site, the right lumbar lymph node (draining lymph node) and the spleen of mice. The inflammatory cell infiltrate seen in the tissues of the intramuscular injection sites (infiltrates of lymphocytic/mononuclear inflammatory cells) were caused by the intramuscular injection of the vaccine with the increased germinal centre development of the right lumbar lymph node caused by immune stimulation of the lymphatic drainage from this area and are not considered adverse.

4.8 Other toxicity Studies

No other toxicity studies with AZD1222 were conducted.

5 INTEGRATED OVERVIEW AND CONCLUSIONS

AZD1222 has been shown to be immunogenic in BALB/c, CD-1 mice, ferrets, non-human primate (NHP) and pig models. Whilst a single dose of AZD1222 induced antigen-specific antibody and T cell responses, a booster immunisation enhanced antibody responses, particularly in pigs, with significant increases in SARS-CoV-2 neutralising antibody titres (Graham et al 2020). A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated ERD. A single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to vector controls (van Doremalen et al 2020). Importantly, no evidence of ERD following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed (van Doremalen et al 2020).

Biodistribution studies with similar ChAd vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice have previously been performed and showed no evidence of replication of the virus or presence of disseminated infection after IM injections. WHO guidelines on nonclinical evaluation of vaccines states that pharmacokinetic studies (eg, for determining serum or tissue concentrations of vaccine components) are normally not needed and specific studies should be

considered on a case-by-case basis (eg, when using novel adjuvants or alternative routes of administration).

A biodistribution study using the ChAdOx1 vector with a hepatitis B virus (HBV) insert following IM injection on days 1 and 28 in mice has been conducted. This study shows distribution to some samples of all tissues on days 2 and 29. The highest levels (copies/mg sample) were noted at the site of administration (skeletal muscle), ranging from 3×10^8 to 9.97×10^9 copies/mg sample. In the majority of samples of other tissues taken on Day 56, the levels were below the level of quantification, indicating elimination. AZD1222 is made using a platform technology utilized for other previously studied investigational vaccines and is sufficiently characterized to use toxicology data with other vaccines that use the same platform (Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance for Industry, June 2020 FDA 2020). Administration of a related betacoronavirus (MERS-CoV) ChAdOx1 vectored vaccine expressing full-length S protein was associated with treatment related changes in the right lumbar lymph node, spleen and intramuscular injection site. The spectrum and severity of the changes were consistent with the administration of an antigenic substance such as ChAdOx1 MERS which were considered to be non-adverse. This was also true for the similar replication-defective ChAd vaccines, ChAd OX1 NP+M1 and AdCh63 MSP-1.

In the mouse cardiovascular and respiratory safety pharmacology study there were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters considered to be AZD1222-related. Irwin Screen observations showed no effects considered to be AZD1222-related.

In the repeat dose (once every 3 weeks over a 43 day period) toxicity study in CD-1 mice, AZD122 was well tolerated, with a transiently higher body temperature in males, decreases in monocytes in males and females (consistent with the expected pharmacology of AZD1222) and increase in globulin and decrease in albumin and albumin/globulin ratio, consistent with an acute phase response, observed. In all animals dosed with AZD1222, antibodies against the S-glycoprotein were raised and maintained throughout the dosing and recovery periods in all animals. In AZD1222 animals, higher spleen weights were observed but with no correlating macroscopic or microscopic changes. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with AZD1222 which were consistent with the anticipated findings after intra-muscular injection of vaccines.

In the preliminary DART study in mice, there were no AZD1222-related effects seen for dams in-life including at the injection site, for female reproduction, fetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no AZD1222-related fetal visceral or skeletal findings.

In conclusion, AZD1222 and similar ChAd vaccines are well tolerated and are not associated with any adverse effects in mice. Further, similar ChAd vaccines show no evidence of replication or dissemination after IM injection in mice. AZD1222 is immunogenic in mice, ferrets, NHP and pig models inducing humoral and cellular immune responses. Vaccination with AZD1222 significantly reduced viral load following a SARS-CoV-2 challenge in rhesus macaques with no evidence of ERD.

6 REFERENCES

Acosta et al 2015
Acosta PL, Caballero MT, Polack FP. Brief History and Characterization of Enhanced Respiratory Syncytial Virus Disease. Clin Vaccine Immunol 2015;23(3):189-95 (CRA)

Arvin et al 2020
Arvin AM, Fink K, Schmid MA, Cathcart A, Spreafico R, Havenar-Daughton C et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020;584(7821):353-63.

Castro and Clatworthy 2020
Castro-Dopico T, Clatworthy MR. IgG and Fcgamma Receptors in Intestinal Immunity and Inflammation. Front Immunol. 2019;10805.

Dahiya et al 2020
Dahiya DS, Kichloo A, Albosta M, Pagad S, Wani F. Gastrointestinal implications in COVID-19. J Investig Med. 2020.

FDA 2020
Food and Drug Administration. Center for Biologics Evaluation and Research Development and Licensure of Vaccines to Prevent COVID-19. https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/development-and-licensure-vaccines-preventcovid-19

Graham et al 2020
Graham SP, McLean RK, Spencer AJ, Belij-Rammerstorfer S, Wright, D, Ulaszewska M, et al. Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19. BioRxiv 2020; Preprint Version 1:1-11

ICMRA 2020
International Coalition of Medicines Regulatory Authorities. Global regulatory workshop on COVID-19 vaccine development. Summary Report.

http://www.icmra.info/drupal/sites/default/files/2020-03/First%20regulatory%20COVID-19%20workshop%20-%20meeting%20report_March%202020.pdf

Munster et al 2020
Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Perez-Perez L, Schulz J et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature. 2020;585(7824):268-72.

Sellers et al 2020
Sellers RS, Nelson K, Bennet B, Wolf J, Tripathi N, Chamanza R et al. Scientific and Regulatory Policy Committee Points to Consider*: Approaches to the Conduct and Interpretation of Vaccine Safety Studies for Clinical and Anatomic Pathologists. Toxicol Pathol. 2020;48(2):257-76.

van Doremalen et al 2020
van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. BioRxiv 2020;Preprint Version 1:1-23

Villapol 2020
Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res. 2020;22657-69.

WHO 2005
WHO. (World Health Organization) WHO Technical Report Series, No 927. Annex 1. WHO guidelines on nonclinical evaluation of vaccines. https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1 Published 2005. Accessed 26 May 2020.

WHO 2013
WHO. (World Health Organization) Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. https://www.who.int/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf?ua=1

Yang et al 2020
Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. Lancet Gastroenterol Hepatol. 2020;5(7):629-30.

Zhang et al 2020
Zhang L, Jackson CB, Mou H, Ojha A, Rangarajan ES, Izard T et al. The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity. bioRxiv. 2020.

Zhong et al 2020
Zhong P, Xu J, Yang D, Shen Y, Wang L, Feng Y et al. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. Signal Transduct Target Ther. 2020;5(1):256.

2.4. Nonclinical Overview

Drug Substance	AZD1222
ANGEL ID	Doc ID-004493554
Date	26 April 2021

2.4 Nonclinical Overview AZD1222

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

AstraZeneca (the Sponsor) is developing AZD1222 for the prevention of coronavirus disease-2019 (COVID-19). AZD1222 is a recombinant chimpanzee adenovirus (ChAd) expressing the severe respiratory syndrome-coronavirus-2 (SARS CoV-2) spike (S) surface glycoprotein. Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford with subsequent transfer of development activities to the Sponsor.

AZD1222 is a recombinant replication-defective ChAd vector expressing the SARS CoV-2 S surface glycoprotein, driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator (tPA) leader sequence at the N terminus. Spike (S) is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the SARS-CoV-2 virion. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 (ACE-2) binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S in receptor binding and membrane fusion make it a desirable target for vaccine and antiviral development. AZD1222 expresses a codon-optimised coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947.

The ChAdOx1 platform technology, as well as other ChAd related vaccines, were used to support the first-in-human (FIH) and other early clinical AZD1222 studies. This approach of using platform data to support a FIH clinical study is consistent with the views expressed by global regulators at the International Coalition of Medicines Regulatory Authorities – Global Regulatory Workshop on COVID-19 vaccine development, 18 March 2020 (ICMRA 2020). To support the FIH study, biodistribution studies with similar replication-defective ChAd vaccines (AdCh63 ME TRAP and AdCh63 MSP-1) and toxicology studies with a related betacoronavirus (MERS-CoV) ChAdOx1 vectored vaccine expressing full-length S protein, as well as other ChAd related vaccines (AdCh63 MSP-1, ChAd OX1 NP+M1) in mice were used (Table 2).

To date, immunology and biological activity studies (including prime boost vaccination) of AZD1222, have been conducted in mice, non-human primates, ferrets and pigs (Table 1). A mouse cardiovascular and respiratory safety pharmacology study has also been conducted with AZD1222, along with Irwin assessment as part of the repeat-dose toxicity study.

To support licensure, biodistribution studies with AZD1222 IM (Table 1) or ChAdOx1 HBV IM (Table 2) and toxicology studies with AZD1222 were conducted, which included a Good Laboratory Practice (GLP) repeat-dose toxicity and 2 GLP embryo-fetal development (EFD) studies in CD-1 mice (Table 1).

All pivotal nonclinical safety studies were conducted in OECD member countries and in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP), and according to relevant International Conference on Harmonisation guidelines.

Table 1 List of Nonclinical Studies with AZD1222

Study (Report Number or publication)	Species	Dose and route of administration	Sponsor / Test Facility	GLP Y/N
Primary Pharmacology				
Effect of D614G Mutation in SARS-CoV-2 Spike Protein on AZD1222 (20-01700)	In vitro	NA	Jenner University of Oxford / CSIRO Health and Biosecurity, Australia	N
Murine Immunogenicity (van Doremalen et al 2020)	Balb/C and CD-1 mice	Single dose, IM 6×10^9 vp AZD1222 or Control - ChAdOx1 GFP	Jenner Institute - Oxford University, UK / NIH, MT, USA	N
Murine Immunogenicity (Graham et al 2020)	Balb/C and CD-1 mice	Day 0 and 28 or 28 only IM, 6.02×10^9 vp AZD1222	Jenner Institute – University of Oxford / Pirbright Institute, UK	N
Non-human Primate Efficacy and Immunogenicity (van Doremalen et al, 2020)	Rhesus macaques	Day -56 and -28 or -28 only before challenge, IM 2.5×10^{10} vp AZD1222 or Control - ChAdOx1 GFP	Jenner Institute - University of Oxford, UK / NIH, USA	N
Efficacy of ChAdOx1 nCoV-19 Against Coronavirus Infection in Rhesus Macaques (6284)	Rhesus macaques	Single dose, Day -27 before challenge, IM 2.5×10^{10} vp AZD1222, or Control – PBS	Jenner Institute - University of Oxford / Public Health England, Porton Down, UK	N
Assessment of Efficacy of SARS-CoV-2Vaccine Candidates in the Ferret Model (20-01125)	Ferret	Day -56 and -28 or -28 only before challenge, IM, IN 2.5×10^{10} vp AZD1222, or Control – PBS	Jenner University of Oxford / CSIRO Health and Biosecurity, Australia	N

Table 1 List of Nonclinical Studies with AZD1222

Study (Report Number or publication)	Species	Dose and route of administration	Sponsor / Test Facility	GLP Y/N
Efficacy of ChAdOx1 nCoV-19 Against Coronavirus Infection in Ferrets (6285)	Ferret	Day -56 and -28 or -28 only before challenge, IM 2.5 x 10^{10} vp AZD1222, or Control - ChAdOx1 GFP or Day -14, IM, formalin-inactivated SARS CoV-2	Jenner Institute - University of Oxford / Public Health England, Porton Down, UK	N
Porcine Immunogenicity (ar001111 / Graham et al 2020)	White-Landrace-Hampshire cross-bred pigs	Day 0 and 28, IM 5.12 × 10^{10} vp AZD1222	Jenner Institute - University of Oxford / Pirbright Institute, UK	N
ChAdOxl-nCoV19 immunopotency assay (INT-ChadOx1 nCov19-POT004)	Balb/C and CD-1 mice	5 × 10^{9} vp AZD1222	Jenner Institute – University of Oxford, UK	N
Safety Pharmacology				
Cardiovascular and Respiratory Assessment Following Intramuscular Administration to Male Mice (617078)	CD-1 mice	Day 4, IM 2.59 x 10^{10} vp AZD1222 or IP, 1 mg/kg, Salbutamol (0.9% w/v sodium chloride) and Day 1, IM, A438 buffer,	AstraZeneca / Charles River Laboratories Ltd, UK	Y
Distribution				
AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse (514559)	CD-1 mice	Single dose, IM 3.7 x 10^{10} vp AZD1222,	AstraZeneca / Charles River Laboratories Ltd, UK	Y
Repeat Dose Toxicology				
AZD1222 (ChAdOx1-nCovd-19): A 6 Week Intermittent Dosing Intramuscular Vaccine Toxicity Study in the Mouse with a 4 Week Recovery (513351)	CD-1 mice	Days 1, 22 and 43, IM 3.7 x 10^{10} vp AZD1222	AstraZeneca / Charles River Laboratories Ltd, UK	Y

Table 1 List of Nonclinical Studies with AZD1222

Study (Report Number or publication)	Species	Dose and route of administration	Sponsor / Test Facility	GLP Y/N
Developmental and Reproductive Toxicology				
ChAdOx1-nCovd19: A Preliminary Intramuscular Injection Vaccine Development and Reproductive Study in Female CD-1 Mice (490838)	CD-1 mice	Day 1 (13 days prior to pairing for mating) and GD 6 to EFD phase animals and on GD 6 and GD 15 to littering phase animals, IM 2.59×10^{10} vp AZD1222 or Control – A438 buffer	AstraZeneca / Charles River Laboratories Ltd, UK	Y
AZD1222 (ChAdOx1 - nCovd19): An Intramuscular Vaccine Development and Reproductive Study in Female CD-1 Mice (490843)	CD-1 mice	Day 1 (13 days prior to pairing for mating) and GD 6 to EFD phase animals and on GD 6 and GD 15 to littering phase animals, IM 3.71×10^{10} vp AZD1222 or Control[b]	AstraZeneca / Charles River Laboratories Ltd, UK	Y

CSIRO = Commonwealth Scientific and Industrial Research Organisation, Geelong, Australia; EFD = embryo-foetal development; GD = gestation day; IM = intramuscular; IN = intranasal; NIH = National Institute of Health

[a] AZD1222 Vehicle (10 mM histidine, 7.5% [v/w] sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% [v/w] Polysorbate-80, 0.1 mM EDTA and 0.5% [v/w] ethanol, pH 6.6)

Table 2 List of Nonclinical Studies with Similar Replication-defective ChAd Vaccines (AdCh63 and ChAdOx1)

Study (Report Number)	Species	Dose and route of administration	Source	GLP Y/N
AdCh63 MSP-1 and MVA MSP-1 Tissue Distribution Study By Intra-Muscular Administration To Mice (Report UNO0014/RMBIODIST-001)	Balb/C mice	Day 1, IM 1.11×10^{10} vp AdCh63 MSP-1 1.04×10^{8} pfu MVA MSP-1	Jenner Institute – University of Oxford / Huntingdon Life Sciences,[a] UK	Y[b]
AdCh63ME-TRAP Tissue Distribution Study By Intra-Dermal Administration To Mice (UNO0009/MAB-001)	Balb/C mice	Day 1, ID 3.3×10^{9} vp	Jenner Institute – University of Oxford / Huntingdon Life Sciences,[a] UK	Y[b]
ChAdOx-1 HBV and MVA-HBV Biodistribution Study in BALB/c Mice with Shedding Assessment (0841MV38.001)	Balb/C mice	Days 1 and 28, IM 2.4×10^{10} vp ChAdOx-1-HBV 6.1×10^{7} pfu MVA-HBV	Jenner Institute – University of Oxford / Calvert Laboratories, USA	Y
ChAdOx1 Chik Vaccine or ChAdOx1 MERS: Toxicity Study by Intramuscular Administration to Mice (QS18DL)	Balb/C mice	Day 1 and 15, IM 1×10^{10} vp	Jenner Institute – University of Oxford / Envigo CRS Limited UK	Y
ChAd OX1 NP+M1 and MVA NP+M1: Toxicity Study by Intramuscular Administration to Mice (XMM0003)	Balb/C mice	Day 1, IM ChAd OX1 NP+M1 1×10^{10} vp and Day 15, IM MVA NP+M1 1.5×10^{7} pfu	Jenner Institute – University of Oxford / Huntingdon Life Sciences,[a] UK	Y

Table 2 List of Nonclinical Studies with Similar Replication-defective ChAd Vaccines (AdCh63 and ChAdOx1)

Study (Report Number)	Species	Dose and route of administration	Source	GLP Y/N
Mouse Toxicity AdCh63 MSP-1 and MVA MSP-1 or a Combination of AdCh63 ME-TRAP and MVA ME-TRAP (UNO0013)	Balb/C mice	Day 1, IM AdCh63 MSP-1 1.11×10^{10} vp Day 15, IM MVA MSP -1 10.4×10^{7} pfu Day 1 and 15, IM AdCh63ME-TRAP/ MVA ME TRAP 0.78×10^{10} vp / 6.85×10^{7} pfu	Jenner Institute – University of Oxford / Huntingdon Life Sciences,[a] UK	Y

[a] Currently Covance CRS Ltd.
[b] In-life phase conducted to GLP; biodistribution phase (RBIODIST-001 or MAB-001) not conducted to GLP

2 PHARMACOLOGY

2.1 Primary Pharmacodynamics

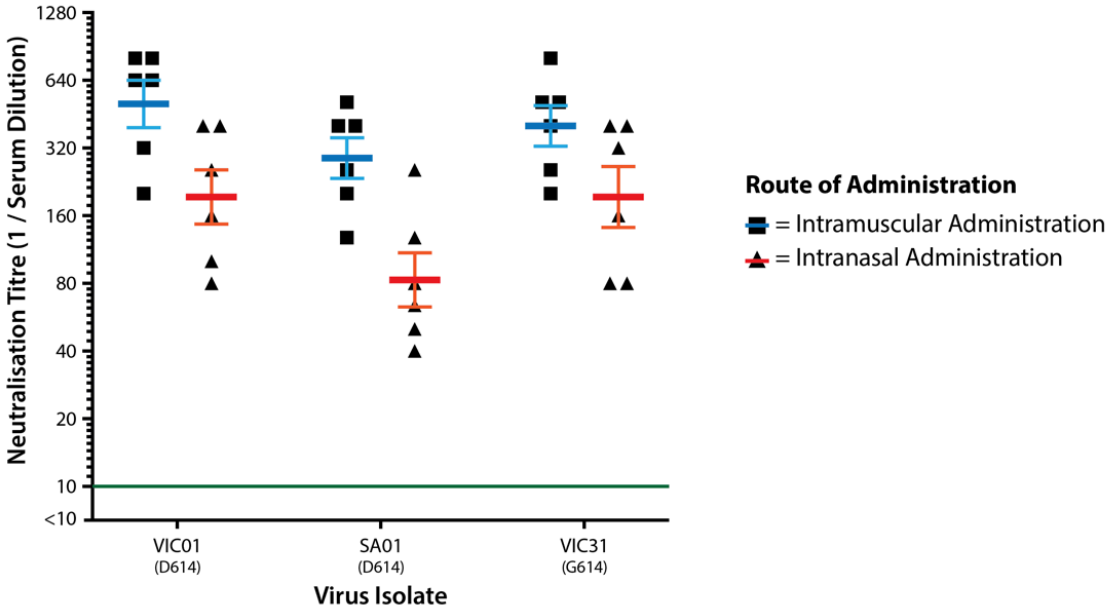
Immunogenicity studies in animal models responsive to AZD1222 were conducted to evaluate the immunologic properties of this COVID-19 vaccine candidate to support FIH clinical trials. AZD1222 has been shown to be immunogenic in BALB/c, CD-1 mice, ferrets, non-human primate (NHP) and pig models. These studies included evaluation of humoral, cellular and functional immune responses. Whilst a single dose of AZD1222 induced antigen-specific antibody and T cell responses, a booster immunisation enhanced antibody responses, particularly in pigs, with significant increases in SARS-CoV-2 neutralising antibody titres (Graham et al 2020). A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated enhanced respiratory disease (ERD). A single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to vector controls (van Doremalen et al 2020). Importantly, no evidence of ERD following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed (van Doremalen et al 2020).

Mutations are occurring naturally within the SARS-CoV-2 genome. Most vaccines in development rely upon inducing immune responses towards Spike protein (S), the main virus surface protein. A D614G mutation in S is increasing in prevalence amongst sequenced

viruses worldwide. The mutation is thought to increase infectivity of the virus by reducing S1 shedding, increasing infection (Zhang et al 2020). The effect of the D614G mutation on the efficacy of virus neutralisation following vaccination of ferrets with AZD1222 was assessed in study 20-01700 (Figure 1). A new Australian isolate containing the D614G mutation (VIC31) was obtained from VIDRL. Three isolates were used for virus neutralisation assays: SA01: has identical amino acid sequence in S to Wuhan-Hu-1. VIC01: S differs from SA01 by an Ser247Arg mutation. VIC31: S differs from SA01 by the Asp614Gly mutation.

Overall, there were no significant effects of the D614G mutation in the SARS-CoV-2 Spike protein on relative neutralisation of D614 and G614 variants with serum samples collected from ferrets that had received prime-boost administrations of AZD1222. Therefore, animal challenge studies presented are relevant to strains circulating in the human population.

Figure 1 Effect of D614G mutation on vaccine-induced antibody-mediated neutralisation.



Mean neutralising titres (calculated from log2-values) to three circulating Australian SARS-CoV-2 isolates. Neutralisation titres of serum samples collected following prime-boost vaccination with AZD1222 in ferrets, administered by two routes (intramuscular and intranasal). Bold horizontal lines represent overall mean titre of the vaccination route/isolate combination with uncertainty bars representing Standard Error of the Mean (SEM). Square and triangle marks represent mean titres of the triplicate titres for each serum sample/isolate combination.

Viral RNA in Gastrointestinal Tract

In the NHP pharmacology study (van Doremalen et al 2020), there was an unexpected finding of viral RNA in tissues of the gastrointestinal (GI) tract at 7 days post-challenge in immunised, but not control, animals. Viral gRNA load in intestinal tissues of prime-boost-vaccinated animals was higher than the levels measured in control and prime-only-vaccinated animals at 7 days post-challenge and was associated with the detection of sgRNA. However, no infection of intestinal tissue was observed by immunohistochemistry, nor were we able to detect infectious virus in intestinal tissue. Given that spike-specific antibodies were significantly increased after the second immunization (two-tailed signed-rank Wilcoxon test) higher viral gRNA load intestinal in prime-boost animals may correlate with greater intestinal clearance and retention of opsonised virus following challenge. FcRn allows the entry and retrieval of IgG from the intestinal lumen throughout health and disease. This bidirectional transport allows the secretion of IgG into the lumen, the subsequent uptake of opsonized bacteria and viruses (Castro and Clatworthy 2020). As previously reported, SARS-CoV-2 antigen can be detected in lymphocytes and macrophages in the lamina propria of the intestinal tract of control animals (Munster et al 2020). This may indicate a higher proportion of plasma cells secreting IgA2 in the gut lamina propria of prime-boost-vaccinated animals and trapping of SARS-CoV-2 virus. Whilst SARS-CoV-2 virus may make its way to the gastric lumen, it would be subjected to the adverse effect of the acidic environment of the stomach that would significantly affects viability.

Nevertheless, SARS-CoV-2 can cause gastrointestinal symptoms, such as loss of appetite, vomiting, diarrhoea, or abdominal pain during the early phases of the disease (Villapol 2020). It has been reported in some patients that although SARS-CoV-2 has been cleared in the respiratory tract, the virus continues to replicate in the gastrointestinal tract and could be shed in faeces (Yang et al 2020). Currently, the exact mechanism of SARS-CoV-2 interaction with the gastrointestinal tract is still not fully understood. However, SARS-CoV-2 shows a high affinity to ACE2 receptors, making sites of high ACE2 receptor expression such as lungs and GI tract prime targets for infection (Dahiya et al 2020). It is therefore possible that gastrointestinal symptoms in COVID-19 are somehow caused by the direct attack of SARS-CoV-2 to gastrointestinal tract (Zhong et al 2020). If higher viral gRNA loads in intestinal tissues of prime-boost vaccinated animals is associated with continued replication then it was not associated with any signs of lesions or infection.

Lung Histopathology

In rhesus macaques 3 out of 6 control animals developed some degree of viral interstitial pneumonia following SARS-CoV-2 challenge. Lesions were widely separated and characterised by thickening of alveolar septum. Alveoli contained small numbers of pulmonary macrophages and rarely oedema. Type-II pneumocyte hyperplasia was observed. No histological lesions were observed in the lungs of vaccinees.

In comparison, the majority of histopathological findings made in the lungs of ferrets following SARS-CoV-2 challenge were modest at most. In control group 3a that received a prime with ChAdOx1 vector expressing green fluorescent protein (GFP) one ferret showed mild lesions compatible with acute bronchiolitis and the other animals were similar to group 1 primed with AZD1222. Only mild inflammatory cell foci and no lesions were observed in group 1. In group 2 that received a prime and boost with AZD1222, inflammatory cell were also detected in lungs. These changes are likely associated with an immune response to challenge as they were also observed in controls. In group 4 immunised with inactivated SARS CoV-2, mild to moderate lesions were observed in the lungs with inflammatory cells and perivascular cuffing at day 7 post challenge potentially indicative of enhanced respiratory disease. In a second ferret study, no significant histological lung changes were present in any of the animals examined.

Enhanced respiratory disease (ERD) can result from immunization with antigen that is not processed in the cytoplasm, resulting in a nonprotective antibody response and CD4+ T helper priming in the absence of anti-viral cytotoxic T lymphocytes. This type of vaccine response can lead to a pathogenic Th2 memory response with eosinophil and immune complex deposition in the lungs after respiratory infection. For example, infants and toddlers immunized with a formalin-inactivated virus vaccine against respiratory syncytial virus (RSV) experienced an enhanced form of RSV disease characterized by high fever, wheezing and bronchopneumonia when they became infected with wild-type virus in the community (Acosta et al 2015). AZD1222 not expected to cause ERD because antigens are expressed intracellularly, generating anti-viral cytotoxic T cell and protective antibody responses.

In the van Doremalen et al study, significantly reduced viral load in the bronchoalveolar lavage fluid and lower respiratory tract tissue of vaccinated rhesus macaques challenged with SARS-CoV-2 with no pneumonia was observed compared to control animals. No evidence of immune-enhanced disease after viral challenge in vaccinated SARS-CoV-2-infected animals was found in terms of increased severity of viral infection. At present, there are no known clinical findings, immunological assays or biomarkers that can differentiate any severe viral infection from immune-enhanced disease, whether by measuring antibodies, T cells or intrinsic host responses (Arvin et al 2020). Carefully controlled human studies of sufficient size to enable the detection of increased frequency of severe cases in vaccinated cohorts compared to control group are required to determine if antiviral host responses may become harmful in humans.

In conclusion, the rhesus macaque is more predictive than ferret of histological lung changes and the ability of immunisation with AZD1222 to mitigate these following challenge with SAR-CoV-2. No enhanced respiratory disease was observed post challenge in AZD1222 immunised animals.

2.2 Secondary Pharmacodynamics

Secondary pharmacodynamic studies have not been conducted with AZD1222.

2.3 Safety Pharmacology

In a mouse cardiovascular and respiratory safety pharmacology study, a group of 8 male CD-1 mice were dosed by IM injection with the control item for AZD1222 (A438 buffer) on Day 1 and AZD1222 (2.59 x 10^{10} vp dose) on Day 4 (617078).

There were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters considered to be AZD1222-related. The No Observed Effect Level (NOEL) for cardiovascular and respiratory assessment was an AZD1222 dose of 2.59 x 10^{10} vp .

Irwin Screen observations (autonomic, neuromuscular, sensorimotor, behavioural parameters) and effects on body temperature and pupil size were made in the repeat-dose IM toxicity study (513351) in male and female CD-1 mice on Days 8 and 29 following administration of AZD1222 at 3.7 x 10^{10} vp on Days 1, 22. There were no effects on body temperature, pupil size or Irwin Screen observations considered to be AZD1222-related.The NOEL for the Irwin Screen phase was 3.7 x 10^{10}.

2.4 Pharmacodynamic Drug Interactions

Pharmacodynamic drug interaction studies have not been conducted with AZD1222.

3 PHARMACOKINETICS

3.1 Absorption

Absorption studies evaluations are not generally needed for vaccines. WHO guidelines on nonclinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune responses.

3.2 Distribution

Distribution studies are not generally needed for vaccines. WHO guidelines on nonclinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), states that traditional ADME evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response.

In an AZD1222 biodistribution study in mice, there was no biodistribution to blood and faeces samples with the exception of low signal from 2 blood and 1 faeces samples on Day 2. Both blood samples had signals below the limit of quantification (<LLOQ) and the faeces sample returned a low signal of 1.30 x 10^3 copies/µg DNA (LLOQ was 50 copies/Q-PCR reaction). In tissues, AZD1222 vector DNA showed biodistribution to the intramuscular administration sites, sciatic nerve, bone marrow, liver, lung and spleen. The highest levels of AZD1222 vector DNA (10^3 to 10^7 copies/µg DNA) were observed in the intramuscular administration sites and sciatic nerve (close proximity to the administration sites) on Day 2. Lower levels of AZD1222 vector DNA (<LLOQ to 10^4 copies/µg DNA) were observed in bone marrow, liver, spleen and lung, on Day 2. The levels of AZD1222 and the number of tissues with detectable levels of AZD1222 vector DNA decreased from Day 2 to 29, indicating elimination.

A biodistribution and shedding study using the ChAdOx1 vector with an hepatitis B virus (HBV) insert after IM injection on Days 1 and 28 in mice was conducted (0841MV38.001). Distribution to some samples of all tissues was noted on day 2 and Day 29. The highest levels (copies/mg sample) were noted at the site of administration (skeletal muscle), ranging from 3 x 10^8 to 9.97 x 10^9 copies/mg sample. In the majority of samples of other tissues taken on Day 56, the levels were below the level of quantification, indicating elimination. Low levels were noted in 1 sample (of 6) for each of heart and liver, 1 of 3 for ovary and testes, and 3 of 6 lymph node samples at this timepoint.

Biodistribution studies with similar ChAd vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice have previously been performed and showed no evidence of replication of the virus or presence of disseminated infectious virus after IM injections.

3.3 Metabolism

Metabolism studies have not been conducted with AZD1222. The expected consequence of metabolism of biotechnology-derived vaccines is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood.

3.4 Excretion

Excretion studies have not been conducted with AZD1222. No virus excretion is expected with AZD1222 as it is a non-replicating vaccine vector. Shedding of ChAdOx1 HBV in mice following IM administration of Days 1 and 28 have been assessed. DNA was extracted from mouse fecal and urine samples collected were all negative, suggesting that no shedding had occurred in these matrices at the times sampled.

3.5 Pharmacokinetic Drug Interactions

Pharmacokinetic drug interaction studies have not been conducted with AZD1222.

3.6 Other Pharmacokinetic Studies

Other pharmacokinetic studies have not been conducted with AZD1222.

4 TOXICOLOGY

4.1 SINGLE DOSE TOXICITY

No single dose toxicity studies have been performed with AZD1222.

4.2 REPEAT DOSE TOXICITY

A 6-week repeat-dose GLP toxicity study with AZD1222 in mice was conducted.

As the ChAdOx1 platform technology utilized for AZD1222 is well characterized, toxicology data with ChAdOx1 MERS-CoV vaccine expressing the full-length Spike protein in mice (Report QS18DL), was used to support first in human (FIH) clinical trials for AZD1222 (International Coalition of Medicines Regulatory Authorities – Global Regulatory Workshop on COVID-19 vaccine development, 18 March 2020 [ICMRA 2020]). In addition, toxicology studies on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) are also discussed.

At the time of toxicology species selection only ChAdOx1 immunogenicity data for mouse and rhesus macaques was available to the sponsor. Pig and ferret immunogenicity data were subsequently made available. Given that both mouse and NHP elicit appropriate immune responses to AZD1222 and considering the need to expedite toxicity testing, the mouse was selected as the toxicology species given the urgency of the ongoing pandemic, the longer lead time for NHP toxicity studies and longer reproductive toxicity study requirements. For dosing considerations, the CD-1 mouse strain was selected due to its larger size compared to the Balb/c mouse strain.

4.2.1 A 6 -Week Intermittent Dosing Intramuscular AZD1222 Toxicity Study in Mice with a 4 Week Recovery

The objective of this study was to determine the potential toxicity of AZD1222 (total viral particle dose of $3.7x10^{10}$) when given by intramuscular injection intermittently (on Days 1, 22 and 43) to mice, with a 28 day recovery period to evaluate the potential reversibility of any findings (513351). In addition, the immunogenicity was evaluated. Scheduled necropsies were conducted either at the end of the 6 week treatment period (Day 45) or at the end of the 28 day recovery period.

The following parameters and end points were evaluated in this study: clinical signs, body temperature, body weights, body weight gains, food consumption, dermal scoring, Irwin

screen observations, clinical pathology parameters (hematology and plasma chemistry), immunogenicity, gross necropsy findings, organ weights, and histopathological examinations.

In comparison to controls and pre-study data, a slightly higher body temperature was observed in AZD1222 treated males, notably on Days 22, 4 hours post dose (range 36.2-39.5^{o}C compared to 36.2-38.7^{o}C in controls) but was comparable to controls by 24 hours post-dose. There was no AZD1222-related change in body temperature recorded in males, as part of the Irwin observations.

In animals administered AZD1222, there was a mild decrease in monocytes on Day 45, which was consistent with expected pharmacology following immunisation. Additionally, globulin was mildly higher, and albumin and albumin/globulin ratio were minimally to mildly lower, which was consistent with an acute phase response. Following the recovery period, globulin remained mildly higher and albumin/globulin ratio remained mildly lower in AZD1222-treated females, the other changes had reversed.

All samples collected from animals during the pre-treatment phase prior to immunisation were below the limit of quantification (BLQ) for the assay (BLQ; 0.250 AU/mL) and considered seronegative. Samples collected indicate that all animals mounted an antibody response to S-glycoprotein following a single administration of AZD1222 on Day 1 with most animals showing a marked increase in the level of antibody response following a second administration of AZD1222 on Day 22. On Day 74, a further increase in antibody response or maintenance of response was observed in all animals following a third administration of AZD1222.

At histopathological examination of the main study animals, mononuclear and/or mixed cell inflammation was observed in the subcutaneous tissue and underlying skeletal muscle at the control and AZD1222 administration sites. This finding was of a higher incidence in animals dosed with AZD1222. In some animals there was an extension of the inflammatory cells into the fascia and connective tissue below the skeletal muscle at the administration sites, that extended to surround the sciatic nerve. The inflammatory cells did not extend into the endoneurium of the sciatic nerve and no findings were present in the underlying axons, which appeared histologically normal. Inflammatory cells were not observed in the nerve roots contained within the lumbar spinal cord sections, confirming that the epineurial/perineurial inflammatory cells noted in the sciatic nerve samples resulted from an extension of the inflammation from the adjacent injection site. There were no findings in the administration sites or sciatic nerves at the end of the recovery period, indicating complete recovery of the AZD1222 related inflammation.

In conclusion, administration of AZD1222 to CD-1 mice (total viral particle dose of 3.7 x 10^{10}) by intramuscular injection on 3 occasions (once every 3 weeks) over a 43 day period was well tolerated, with a transiently higher body temperature in males, decreases in

monocytes in males and females (consistent with the expected pharmacology of AZD1222) and increase in globulin and decrease in albumin and albumin/globulin ratio, consistent with an acute phase response, observed.

In all animals dosed with AZD1222, antibodies against the S-glycoprotein were raised and maintained throughout the dosing and recovery periods in all animals.

In AZD1222 animals, higher spleen weights were observed but with no correlating macroscopic or microscopic changes. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with AZD1222 which were consistent with the anticipated findings after intra-muscular injection of vaccines.

4.2.2 Repeat-dose Toxicology Studies with Similar Replication-defective ChAd Vaccines (AdCh63 and ChAdOx1)

A brief summary of the key findings from the ChAdOx1 MERS vaccine toxicology study in in mice is provided below.

- Changes at the intramuscular injection sites (inflammatory cell infiltrates) were observed in the majority of females and in several males.
- Histopathological changes in the spleen (increased germinal center development) correlated with an increased spleen weight in females. Increased germinal center development of the right lumbar lymph nodes (draining lymph node), correlated macroscopically with enlargement, was observed for the majority of treated animals. Slightly higher circulating white blood cell numbers were observed.
- At the end of the study treatment there was a slightly lower than control body weight gain for treated males and females. For males this was due mainly to slightly lower than control weight gains during Days 15 to 18 however for females this was due mainly to small weight losses during this period. Mice were dosed on Day 1 and 15, with necropsy on day 28.
- Slightly lower group mean liver weight for males and females (0.92X and 0.90X control), higher phosphorus concentration for females (1.2X control) or lower triglyceride concentration for males and females (0.56X and 0.64X) were observed. There was no correlation with histopathological changes.

The spectrum and severity of these changes were consistent with the administration of an antigenic substance such as ChAdOx1 MERS, and were considered to be non-adverse.

Results from the toxicology studies on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) were consistent with ChAdOx1 MERS and were well tolerated with no associated adverse effects. The toxicity data (and toxicity in the target organs) from the ChAdOx1 and ChAd63 based vaccines follows the same pattern, where findings were consistent with a predicted response to vaccine administration.

4.3 Toxicokinetics

Toxicokinetic studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), Pharmacokinetic studies (eg, for determining serum or tissue concentrations of vaccine components) are normally not needed.

4.4 Genotoxicity (Mutagenicity)

Genotoxicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines, (WHO 2005), genotoxicity studies are normally not required for the final vaccine formulation and therefore have not been conducted.

4.5 Carcinogenicity

Carcinogenicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), Carcinogenicity studies are not required for vaccine antigens. AZD1222 is a replication deficient, non-integrating adenovirus vector so there is no risk of carcinogenicity. To date there have been no clinical reports of chromosomal vector integration following adenovirus vector-mediated gene transfer.

4.6 Developmental and Reproductive Toxicity

An evaluation of the impact of AZD1222 on embryo-foetal development was completed in a dose-range study (490838). Intramuscular administration of AZD1222 to groups of CD-1 female mice on Day 1 (13 days prior to pairing for mating) and again on Gestation Day (GD) 6 at 2.59 x 10^{10} vp per occasion (embryofoetal development phase), or on GD 6 and GD 15 at 2.59 x 10^{10} per occasion (littering phase) was well tolerated (490838). Anti-S glycoprotein antibody responses were raised in dams following administration of AZD1222 and these were maintained through the gestational and lactation periods. Seropositivity of foetuses and pups was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively. There were no AZD1222-related effects seen for dams in-life including at the injection site, for female reproduction, foetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no AZD1222-related foetal visceral or skeletal findings.

In the main GLP embryo-foetal development study, IM administration of AZD1222 to groups of CD-1 female mice on Day 1 (13 days prior to pairing for mating) and again on GD 6 at 3.71 x 10^{10} vp per occasion (embryofoetal development phase), or on GD 6 and GD 15 at 3.71 x 10^{10} vp per occasion (littering phase) was well tolerated (490843). Anti-S glycoprotein antibody responses were raised in dams following administration of AZD1222 and these were maintained through the gestational and lactation periods. Seropositivity of fetuses and pups

was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively. There were no test item-related effects seen for dams in-life including at the injection site, for female reproduction, foetal or pup survival, pup physical development and no abnormal gross pathology findings in pups prior to or post weaning or in dams in either phase. There were no test item-related foetal external, visceral or skeletal findings.

4.7 Local Tolerance

Local tolerance of AZD1222 was evaluated as part of the repeat dose toxicity study in mice (513351). There was no erythema or oedema at the injection sites after administration of AZD1222 on any dosing occasion. Histopathology showed minimal subcutaneous oedema was observed in the administration sites in male and female animals from both the control group and those administered AZD1222 and was considered to be related to the route of administration. Minimal mononuclear or mixed cell inflammation was observed in the subcutaneous tissue and underlying skeletal muscle at the administration sites in both male and female animals. This finding was of a higher incidence in animals administered with AZD1222. In some animals there was an extension of the inflammatory cells into the fascia and connective tissue below the skeletal muscle at the administration sites. This resulted in inflammatory cells being noted surrounding the epineurium/perineurium of the sciatic nerve samples. In the hind limb, inflammation around the sciatic nerve due to local extension from the administration site is a well-recognized effect (Sellers et al 2020). Local tolerance was also evaluated as part of a repeat dose GLP toxicology study in mice with the related ChAdOx1 MERS vaccine (QS18DL). Changes related to treatment with ChAdOx1 MERS vaccine were seen in the tissues of the intramuscular injection site, the right lumbar lymph node (draining lymph node) and the spleen of mice. The inflammatory cell infiltrate seen in the tissues of the intramuscular injection sites (infiltrates of lymphocytic/mononuclear inflammatory cells) were caused by the intramuscular injection of the vaccine with the increased germinal centre development of the right lumbar lymph node caused by immune stimulation of the lymphatic drainage from this area and are not considered adverse.

4.8 Other toxicity Studies

No other toxicity studies with AZD1222 were conducted.

5 INTEGRATED OVERVIEW AND CONCLUSIONS

AZD1222 has been shown to be immunogenic in BALB/c, CD-1 mice, ferrets, NHP and pig models. Whilst a single dose of AZD1222 induced antigen-specific antibody and T cell responses, a booster immunisation enhanced antibody responses, particularly in pigs, with significant increases in SARS-CoV-2 neutralising antibody titres (Graham et al 2020). A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated ERD. A single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of

vaccinated animals as compared to vector controls (van Doremalen et al 2020). Importantly, no evidence of ERD following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed (van Doremalen et al 2020).

In the mouse cardiovascular and respiratory safety pharmacology study there were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters considered to be AZD1222-related. Irwin Screen observations showed no effects considered to be AZD1222-related.

In an AZD1222 biodistribution study in mice, there was no biodistribution to blood and faeces samples with the exception of low signal from 2 blood and 1 faeces samples on Day 2. Both blood samples had signals below the limit of quantification (<LLOQ) and the faeces sample returned a low signal of 1.30 x 10^3 copies/µg DNA (LLOQ was 50 copies/Q-PCR reaction). In tissues, AZD1222 showed biodistribution to the intramuscular (IM) administration sites, sciatic nerve, bone marrow, liver, lung and spleen. The highest levels of AZD1222 (10^3 to 10^7 copies/µg DNA) were observed in the IM administration sites and sciatic nerve (close proximity to the administration sites) on Day 2. Lower levels of AZD1222 (<lower limit of quantification [LLOQ] to 10^4 copies/µg DNA) were observed in bone marrow, liver, spleen and lung, on Day 2. The levels of AZD1222 and the number of tissues with detectable levels of AZD1222 decreased from Day 2 to 29, indicating elimination. Biodistribution studies with similar ChAd vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice have previously been performed and showed no evidence of replication of the virus or presence of disseminated infection after IM injections. WHO guidelines on nonclinical evaluation of vaccines states that pharmacokinetic studies (eg, for determining serum or tissue concentrations of vaccine components) are normally not needed and specific studies should be considered on a case-by-case basis (eg, when using novel adjuvants or alternative routes of administration).

A biodistribution study using the ChAdOx1 vector with a hepatitis B virus (HBV) insert following IM injection on days 1 and 28 in mice has been conducted. This study shows distribution to some samples of all tissues on days 2 and 29. The highest levels (copies/mg sample) were noted at the site of administration (skeletal muscle), ranging from 3 x 10^8 to 9.97 x 10^9 copies/mg sample. In the majority of samples of other tissues taken on Day 56, the levels were below the level of quantification, indicating elimination. AZD1222 is made using a platform technology utilized for other previously studied investigational vaccines and is sufficiently characterized to use toxicology data with other vaccines that use the same platform (Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance for Industry, June 2020 FDA 2020). Administration of a related betacoronavirus (MERS-CoV) ChAdOx1 vectored vaccine expressing full-length S protein was associated with treatment related changes in the right lumbar lymph node, spleen and intramuscular injection site. The spectrum and severity of the changes were consistent with the administration of an antigenic

substance such as ChAdOx1 MERS which were considered to be non-adverse. This was also true for the similar replication-defective ChAd vaccines, ChAd OX1 NP+M1 and AdCh63 MSP-1.

In the repeat dose (once every 3 weeks over a 43 day period) toxicity study in CD-1 mice, AZD122 was well tolerated, with a transiently higher body temperature in males, decreases in monocytes in males and females (consistent with the expected pharmacology of AZD1222) and increase in globulin and decrease in albumin and albumin/globulin ratio, consistent with an acute phase response, observed. In all animals dosed with AZD1222, antibodies against the S-glycoprotein were raised and maintained throughout the dosing and recovery periods in all animals. In AZD1222 animals, higher spleen weights were observed but with no correlating macroscopic or microscopic changes. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with AZD1222 which were consistent with the anticipated findings after intra-muscular injection of vaccines.

In the preliminary and main GLP DART studies in mice, there were no AZD1222-related effects seen for dams in-life including at the injection site, for female reproduction, foetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no AZD1222-related foetal visceral or skeletal findings.

In conclusion, AZD1222 and similar ChAd vaccines are well tolerated and are not associated with any adverse effects in mice. Further, similar ChAd vaccines show no evidence of replication or dissemination after IM injection in mice. AZD1222 is immunogenic in mice, ferrets, NHP and pig models inducing humoral and cellular immune responses. Vaccination with AZD1222 significantly reduced viral load following a SARS-CoV-2 challenge in rhesus macaques with no evidence of ERD.

6 REFERENCES

Acosta et al 2015
Acosta PL, Caballero MT, Polack FP. Brief History and Characterization of Enhanced Respiratory Syncytial Virus Disease. Clin Vaccine Immunol 2015;23(3):189-95

Arvin et al 2020
Arvin AM, Fink K, Schmid MA, Cathcart A, Spreafico R, Havenar-Daughton C et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020;584(7821):353-63.

Castro and Clatworthy 2020
Castro-Dopico T, Clatworthy MR. IgG and Fcgamma Receptors in Intestinal Immunity and Inflammation. Front Immunol. 2019;10805.

Dahiya et al 2020
Dahiya DS, Kichloo A, Albosta M, Pagad S, Wani F. Gastrointestinal implications in COVID-19. J Investig Med. 2020.

FDA 2020
Food and Drug Administration. Center for Biologics Evaluation and Research Development and Licensure of Vaccines to Prevent COVID-19. https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/development-and-licensure-vaccines-preventcovid-19

Graham et al 2020
Graham SP, McLean RK, Spencer AJ, Belij-Rammerstorfer S, Wright, D, Ulaszewska M, et al. Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19. BioRxiv 2020; Preprint Version 1:1-11

ICMRA 2020
International Coalition of Medicines Regulatory Authorities. Global regulatory workshop on COVID-19 vaccine development. Summary Report. http://www.icmra.info/drupal/sites/default/files/2020-03/First%20regulatory%20COVID-19%20workshop%20-%20meeting%20report_March%202020.pdf

Munster et al 2020
Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Perez-Perez L, Schulz J et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature. 2020;585(7824):268-72.

Sellers et al 2020
Sellers RS, Nelson K, Bennet B, Wolf J, Tripathi N, Chamanza R et al. Scientific and Regulatory Policy Committee Points to Consider*: Approaches to the Conduct and Interpretation of Vaccine Safety Studies for Clinical and Anatomic Pathologists. Toxicol Pathol. 2020;48(2):257-76.

van Doremalen et al 2020
van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020;586(7830):578-82.

Villapol 2020
Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res. 2020;22657-69.

WHO 2005
WHO. (World Health Organization) WHO Technical Report Series, No 927. Annex 1. WHO guidelines on nonclinical evaluation of vaccines. https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1 Published 2005. Accessed 26 May 2020.

WHO 2013
WHO. (World Health Organization) Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. https://www.who.int/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf?ua=1

Yang et al 2020
Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. Lancet Gastroenterol Hepatol. 2020;5(7):629-30.

Zhang et al 2020
Zhang L, Jackson CB, Mou H, Ojha A, Rangarajan ES, Izard T et al. The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity. bioRxiv. 2020.

Zhong et al 2020
Zhong P, Xu J, Yang D, Shen Y, Wang L, Feng Y et al. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. Signal Transduct Target Ther. 2020;5(1):256.

Clinical Overview	
Drug Name	AZD1222
Date	February 2021

'CONFIDENTIAL'

COVID-19 Vaccine AstraZeneca (AZD1222)

Clinical Overview on AZD1222 Anaphylaxis including Hypersensitivity

Author: [redacted],
Global Safety Physician for AZD1222

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2.

The therapeutic potential of AZD1222 is conferred through expression of the S glycoprotein, and it is designed to stimulate/prime a protective immune response in the recipient towards the SARS CoV-2 virus.

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The vaccine is administered as two IM 0.5 mL doses of 5×10^{10} vp (nominal), at an interval of 4 to 12 weeks.

The purpose of this document is to summarise the key information on which the decision to amend the Core Data Sheet was based, to document the Core Data Sheet amendment, and to support changes to local Prescribing Information.

2 OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4 OVERVIEW OF EFFICACY

This section is not relevant to this document.

5 OVERVIEW OF SAFETY

5.1 Data summary and discussion

Serious Hypersensitivity including anaphylaxis is considered as a potential risk (PR) in the AZD1222 Risk Management Plan (RMP). Based on post-marketing data Hypersensitiviy including Anaphylaxis has been identified as a subject for review by pharmacovigilance processes internal to AstraZeneca.

A search of the safety database was undertaken on 11 February 2021 for cumulative adverse event data (up to 05 February 2021) from available sources (clinical, spontaneous, solicited reporting and literature) using PTs under SMQ narrow Anaphylactic reaction, SMQ narrow Angioedema and PT hypersensitivity in association with the use of AZD1222.

A search of the global Patient Safety database identified 75 case reports of 85 events in patients taking AZD1222. [redacted]

Of cases from post-marketing sources, 11 were reported as non-serious and 64 were reported as serious (36 cases were medically confirmed). There were no fatal reports. All reports were from the UK with the average age of 46 years (range: [redacted] years). Of the 75 reports, 71 were female and 4 were male vaccinees. The adverse events reported in the 75 cases are presented categorised by preferred term (PT) in Table 1 below.

Table 1 Distribution of Reported Adverse Events (AEs)

AE Preferred Term	PT Count	PT Serious Count
Anaphylactic reaction	14	14
Angioedema	7	7
Circulatory collapse	1	1
Eye swelling	5	3
Hypersensitivity	11	11
Lip swelling	7	6
Mouth swelling	2	2
Periorbital swelling	2	2
Pharyngeal swelling	4	3
Shock	2	2
Swelling face	6	3
Swollen tongue	6	5
Urticaria	18	14
Total	**85**	**73**

For all cases discussed below, medical review was done using the Sampson criteria (**Sampson et al 2006**, See Appendix 1 for details of Sampson criteria).

In addition to the Sampson criteria, important aspects of each case were also reviewed including temporal relationship, history of allergies/anaphylaxis, response to EpiPen or steroids.

5.1.1.1 Anaphylaxis

Fourteen out of 75 cases were reported with the PT of anaphylactic reaction. Seven out of these 14 cases met the Sampson criteria for anaphylaxis and these are presented in Table 2 below. 6 of these 7 case reports were reported in females with an age range of [redacted] years. All the reported cases included skin or mucocutaneous manifestations with respiratory or

cardiovascular compromise. Time to onset was within the same day of vaccination for 5 vaccinees and in 2 vaccinees the reactions appeared the following day. [redacted]

Table 2 **Characteristics of Cases of Anaphylactic Reaction Following Receipt of AZD1222 as Reported, fulfilling the Sampson Criteria of Anaphylaxis**

Case #/Country/ Reporter (HCP/ non-HCP)/ Event PT	Vaccinee demo-graphics (years/ gender)	Previous allergy history	Reaction onset	Signs and symptoms	Treatment received (Yes/No) Treatment setting (ED/ In-patient)	Received Epi-nephrine (Yes/No)	Event Outcome	Sampson Criteria (Y/N)	Company comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 **Characteristics of Cases of Anaphylactic Reaction Following Receipt of AZD1222 as Reported, fulfilling the Sampson Criteria of Anaphylaxis**

Case #/Country/ Reporter (HCP/ non-HCP)/ Event PT	Vaccinee demo-graphics (years/ gender)	Previous allergy history	Reaction onset	Signs and symptoms	Treatment received (Yes/No) Treatment setting (ED/ In-patient)	Received Epi-nephrine (Yes/No)	Event Outcome	Sampson Criteria (Y/N)	Company comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 **Characteristics of Cases of Anaphylactic Reaction Following Receipt of AZD1222 as Reported, fulfilling the Sampson Criteria of Anaphylaxis**

Case #/Country/ Reporter (HCP/ non-HCP)/ Event PT	Vaccinee demo-graphics (years/ gender)	Previous allergy history	Reaction onset	Signs and symptoms	Treatment received (Yes/No) Treatment setting (ED/ In-patient)	Received Epi-nephrine (Yes/No)	Event Outcome	Sampson Criteria (Y/N)	Company comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

UK: United Kingdom, HCP: Health Care Professional

The remaining 7 cases did not contain sufficient information to meet the Sampson criteria of anaphylaxis. However, considering temporal relationship between AZD1222 injection and adverse events, the possibility of a causal relationship cannot be excluded. The 7 cases are presented in Appendix 2.

- In 3 cases, vaccinees had prior history of Asthma and allergy had localized rash with respiratory compromise only

[redacted]

Considering the remaining 61 cases reporting PTs under SMQ narrow Anaphylactic reaction, SMQ narrow Angioedema and PT hypersensitivity further information is provided below:

- In 3 cases with the reported PTs of Shock (2), Circulatory collapse (1) there were no other signs and symptoms related to anaphylaxis reported.
- In 2 cases, alternative medical conditions or disease under treatment/background incidence could explain the event.
    - [redacted]
- Two cases included multiple reasons that could explain the reported adverse events:
    - [redacted]
    - [redacted]
- In 48 cases, the time to onset was suggestive of a hypersensitivity reaction, however the information included in the reports, i.e. circumstances leading to the events and concurrent conditions, was not sufficient to confirm anaphylaxis according to Sampson criteria.

- In 3 cases, the time to onset (TTO) of the event is inconsistent with an immediate hypersensitive reaction secondary to the vaccine as the TTO was > 48 hours. These 3 cases identified four adverse events: mouth swelling, lip swelling, periorbital swelling and swelling face.

- In the other 3 cases, the time to onset of reactions is unknown.

5.1.1.2 Angioedema

In 33 of the 75 cases included under SMQ narrow Anaphylactic reaction, SMQ narrow Angioedema and PT hypersensitivity, either Angioedema or a form of local swelling was observed: Angioedema (7), Lip swelling (7), Swelling face (6), Swollen tongue (6), Eye swelling (5), Pharyngeal swelling (4), Mouth Swelling (2), Periorbital swelling (2). In 27 of the 33 cases, time to onset for these events was within 2 days, while for 6 cases, time to onset was either not available or after 4 days of receiving the vaccine.

In 4 of the 7 cases of Angioedema time to onset was less than 24 hours of receiving the vaccine. All 7 cases of angioedema were present in female with age range of 21 to 73 years. All cases were serious, in 6 cases the seriousness criteria was important medical event and in 1 case the seriousness criteria was life threatening.

[redacted]

5.1.2 Literature Search

A search of medical databases up to 05 February 2021 was conducted to obtain information on literature articles about anaphylactic/ anaphylactoid reactions reported in vaccinees receiving COVID-19 Vaccines.

5.1.2.1 Summary of literature findings

Cases of anaphylaxis after administration of the mRNA COVID-19 Vaccines have been reported. The initial estimated reporting rates for anaphylaxis in the US were 11.1 cases per million doses administered of the Pfizer-BioNTech vaccine (14-23 December, 2020) and 2.5 cases per million doses administered of the Moderna vaccine (21 December 2020-10 January 2021). Since these early estimates were generated, millions more doses of both vaccines have been administered and safety monitoring has detected additional cases of anaphylaxis. No deaths from anaphylaxis were reported (**Shimabukuro et al 2021**).

5.1.3 SUMMARY AND CONCLUSION

There were 14 cases of Anaphylaxis (7 cases met the Sampson criteria of Anaphylaxis) reported from post-marketing sources from 3,708,571 doses of AZD1222 administered.

Out of the seven cases that met the widely accepted Sampson criteria, 1 event was reported in male and 6 were reported in females. These 7 vaccinees were in the age range of 28-69 years. Out of the 7 cases, 6 were reported as receiving treatment for the anaphylactic reactions, and 5 received epinephrine. Treatment status is unknown for the remaining 1 case. At the time of reporting, 3 vaccinees had recovered, 3 were recovering and in 1 vaccinee the symptoms were reported as ongoing.

In 33 of the 75 cases either Angioedema or localized oedema/swelling was reported. Time to onset for 69 out of 75 cases was suggestive a possible temporal relationship between AZD1222 and the reported events. For 3 cases, the time to onset of the event was more than 48 hours (however, within 1 week) and for 3 cases the time to onset was unknown. All events were reported after the first dose of AZD1222 vaccine.

Anaphylaxis and Angioedema are reported in medical/scientific literature in association with other COVID-19 vaccines with a possible causal association.

Based on an assessment of available data, AstraZeneca has concluded that there is reasonable possibility of a causal association between AZD1222 and serious hypersensitivity including anaphylaxis/anaphylactic reaction. Therefore, the Core Data Sheet sections 4.4 and 4.8 will be amended to include information on anaphylaxis/anaphylactic reaction and angioedema as an adverse drug reaction associated with AZD1222.

5.2 Exposure

The global post-marketing exposure (by doses distributed by AZ and Serum Institute of India [SII]) to COVID-19 VACCINE ASTRAZENECA was estimated to be 44,496,140 doses as of 31 January 2021.

Vaccine doses administered is a subset of doses distributed. As of 31 January 2021, AstraZeneca received exposure data based on doses administered to vaccinees in United Kingdom (UK). This information is summarised in Table 3 below and it represents the cumulative exposure (by doses administered) up to 31 January 2021. Administration data from SII is not available.

Table 3 COVID-19 VACCINE ASTRAZENECA cumulative exposure (by doses administered), by Region/Country/Collaboration

Region/Country	Exposure by doses administered
United Kingdom	3,708,571

5.3 Estimation of frequency

The frequency of adverse drug reactions is described using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data).

The signal of anaphylaxis was observed in the post-marketing setting. In this setting, it is difficult to calculate an accurate frequency of anaphylaxis since the exposure data is an approximation and the spontaneous cases reported are voluntary and often have limited information or have predisposing / confounding factors for anaphylaxis. Considering the approximation of the patient exposure and voluntary reporting criteria for spontaneous reports, the true frequency of the reported serious hypersensitivity including anaphylaxis events in the post-marketing setting is considered as "not known" (cannot be estimated from the available data).

6 BENEFITS AND RISKS CONCLUSIONS

Based on the quantitative and qualitative evaluation of the currently available post-marketing and clinical safety data, the information regarding anaphylaxis/anaphylactic reaction and angioedema will be added to the CDS. The company will continue to conduct routine pharmacovigilance activities in addition to the ongoing clinical studies as described in AZD1222 Core Risk Management Plan (Version 1.0; dated 15 February 2021) to further characterize this risk.

The benefit of vaccinating with AZD1222 has been weighed against the available safety data from the clinical studies as well as from post-marketing use. An integrated evaluation of the key benefits and risks observed to date did not alter the overall positive benefit-risk balance for the use of AZD1222.

7 REFERENCES

Sampson et al 2006
Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7. doi: 10.1016/j.jaci.2005.12.1303. PMID: 16461139.

Shimabukuro et al 2021
Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021. JAMA. Published online February 12, 2021. doi:10.1001/jama.2021.1967

Appendix 1 Sampson criteria

NIAID/FAAN CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS (Sampson et al 2006)

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced Peak expiratory flow (PEF), hypoxemia)

   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years

Appendix 2 Anaphylaxis case reports which did not fulfill the Sampson criteria for Anaphylaxis

Table 4 Characteristics of Cases of Anaphylactic Reaction Following Receipt of AZD1222, not containing sufficient information to fulfil the Sampson Criteria of Anaphylaxis

Case #/Country/ Reporter (HCP/ non-HCP)/ Event PT	Vaccinee demographic (years/ gender)	Previous allergic history	Reaction onset in minutes/ hours	Signs and symptoms	Treatment received (Yes/No) Treatment setting (ED/In-patient)	Received Epinephrine (Yes/No)	Event Outcome	Comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 **Characteristics of Cases of Anaphylactic Reaction Following Receipt of AZD1222, not containing sufficient information to fulfil the Sampson Criteria of Anaphylaxis**

Case #/Country/ Reporter (HCP/ non-HCP)/ Event PT	Vaccinee demographic (years/ gender)	Previous allergic history	Reaction onset in minutes/ hours	Signs and symptoms	Treatment received (Yes/No) Treatment setting (ED/In-patient)	Received Epinephrine (Yes/No)	Event Outcome	Comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.5 Clinical Overview

Drug Substance AZD1222

Date 25 February 2021

2.5 Clinical Overview

AZD1222 Marketing Authorisation Application

Primary Analysis (Data Cut-off 07 December 2020)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this Clinical Overview:

Abbreviation or special term	Explanation
AdHu5	human adenovirus 5
AE	adverse event
AESI	adverse event of special interest
AZD1222	COVID 19 vaccine AstraZeneca (COVID-19 Vaccine (ChAdOx1-S [recombinant])
BMI	body mass index
CCR7	CC chemokine receptor 7
CD	cluster of differentiation
ChAd63	chimpanzee adenovirus 63
ChAdOx1	chimpanzee adenovirus ox1 (also known as ADVY25)
ChAdOx1 nCoV-19	name of AZD1222 when initially developed by the University of Oxford
ChAdOx1 MERS	chimpanzee adenovirus ox1 with MERS spike antigen
ChAdOx2	chimpanzee adenovirus ox2
CI	confidence interval
COVID-19	coronavirus disease 2019
COVISHIELD	name of AZD1222 manufactured by the Serum Institute of India Private Ltd. (also known as SII-ChAdOx1 nCoV-19).
CSP	Clinical study protocol
DCO	Data cut-off
DP	Drug Product
EDTA	edetate disodium
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
GMFR	geometric mean fold rise
GMR	geometric means response
GMT	geometric mean titre
HAdV-4	Human adenovirus 4
HIV	human immunodeficiency virus
ICH	international council for harmonisation

Abbreviation or special term	Explanation
ICS	intracellular cytokine staining
IFNγ	interferon gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IM	intramuscular(ly)
LD	low dose
M1	influenza A matrix protein 1
MenACWY	meningococcal group a, c, w-135, and y conjugate vaccine
MERS	Middle East respiratory syndrome
MERS-COV	Middle East respiratory syndrome coronavirus
ME-TRAP	multiple epitopes and thrombospondin related adhesion protein
MNA	microneutralisation assay
nAb	neutralising antibodies
NHP	non-human primate
NP	influenza a nucleoprotein
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PRNT	plaque reduction neutralisation test
qPCR	quantitative polymerase chain reaction
RBD	receptor-binding domain
RMP	Risk Management Plan
RNA	ribonucleic acid
RT-PCR	reverse transcription PCR
S	spike
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SD	standard dose
SFC	spot forming cell
Th	T helper
TNFα	tumor necrosis factor alpha

Abbreviation or special term	Explanation
UK	United Kingdom
VAED	vaccine-associated enhanced disease
vp	viral particles
v/v	volume per volume
WHO	World Health Organisation
w/v	weight per volume

CONVENTIONS

Cross-referencing to other documents

Source tables and figures accompany this application; all are located in Module 5.3.5.3. Cross-references to the source data will include the content and analysis category followed by the Table or Figure number. For example, cross-reference to a table with results of the main safety analysis will be cited as: "see Main Safety Table 1.X.X.X."

Cross-references to supplemental tables and figures generated post hoc to support data interpretation will be cited as: "see Supplemental Table IEMTX.X.X."

Cross-references to other sections and modules of the Common Technical Document cite the name of the module (stated in the document header), and the relevant section number (from the main body of the document). Thus, reference to data in Section 4 of the Non-Clinical Overview (see Section 4 of the Non-Clinical Overview) is written as follows: "see Section 2.4.4 of the Non-clinical Overview." Similarly, tables and figures are cross-referred by citing the table or figure number and its location thus "see Table 5, Section 2.4.4 of the Non-clinical Overview."

Data cut-off dates

The DCO date for the primary pooled analyses included in this submission was 07 December 2020 (and will be referred to as "DCO2"). The data cut-off date for the interim pooled analysis included in the original MAA interim analysis submission (04 November 2020) will be referred to as "DCO1."

EXECUTIVE SUMMARY

ChAdOx1-nCoV19 AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tPA leader sequence at the N terminus. AZD1222 is one of the available COVID-19 vaccines—based on different platforms—currently conditionally authorised or authorised for emergency use in several markets after showing significant clinical benefit in this disease. The AZD1222 vaccine was first approved for emergency supply authorisation by the MHRA based on interim efficacy results in a regimen of two standard doses administered 4-12 weeks apart for adults over 18 years of age. Additionally, the AZD1222 vaccine was granted a conditional marketing authorisation from the EMA for the prevention of COVID-19 in people from 18 years of age.

This Clinical Overview presents and discusses key results from the primary analysis as described in the MAA analysis SAP, with a DCO of 07 December 2020 (hereafter referred to as "DCO2"). The pooled primary analysis provided in this updated submission includes data from 4 ongoing blinded, randomised, controlled studies conducted across 3 countries: COV001 (Phase I/II; UK), COV002 (Phase II/III; UK), COV003 (Phase III; Brazil), and COV005 (Phase I/II; South Africa).

The updated primary data, which analysed a larger number of participants, clearly demonstrated that AZD1222 provides protection against severe COVID-19 and COVID-19 hospitalisations, and was consistent with the data presented during the pooled interim analysis in the original submission. No hospitalisations occurred in the AZD1222 group (0/8597) compared to 9 cases in the control group (9/8581) from 15 days after the second dose (SDSD + LDSD) in participants seronegative at baseline. Similarly, complete protection against COVID-19 hospital admission was shown $\geq$ 22 days after the first dose of AZD1222 SD (0 vs 14 cases in Control group, of which two were severe, one with a fatal outcome). These data continue to show the trend seen at DCO1, at which time there was 1 severe case and 9 COVID-19 hospital admission, all in the control group.

When analysing the updated data by country, robust evidence for AZD1222 efficacy emerged for the UK and Brazil studies. In South Africa, a limited number of cases prevented drawing conclusions on vaccine efficacy.

The updated safety data of AZD1222, presented for multiple dosing regimens, by country, as well as in high-risk adult populations of older adults and adults with comorbidities, demonstrated consistency with the safety profile previously shown at the interim analysis.

Overall, the data resulting from the pooled primary analysis demonstrate that vaccine efficacy and safety for AZD1222 are consistent with those presented in the MAA original application,

thus highlighting the strength of the data and the significant clinical value of AZD1222 in addressing the most pressing unmet medical need in a diverse range of populations.

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacological Class

COVID-19 Vaccine AstraZeneca (also known as AstraZeneca COVID-19 vaccine; referred to as AZD1222 throughout this document) is a recombinant replication-deficient chimpanzee adenovirus (ChAd) encoding the SARS-CoV-2 S surface glycoprotein. The therapeutic potential of AZD1222 is conferred through expression of the S glycoprotein, and it is designed to stimulate/prime a protective immune response in the recipient towards the SARS CoV-2 virus. Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford with subsequent transfer of development activities to AstraZeneca (hereafter referred to as "the Applicant").

1.2 Indication and Dosing

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The vaccine is administered IM as two 0.5 mL doses of 5×10^{10} vp (nominal), at an interval of 4 to 12 weeks.

1.3 Scientific Background and Unmet Medical Need

In December 2019, a cluster of patients with pneumonia of unknown cause was discovered in Wuhan, China, and the patients were later confirmed to be infected with the novel coronavirus (CoV) now known as SARS-CoV-2 (Zhou et al 2020). By January 2020, there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. The WHO declared the novel coronavirus a pandemic on 11 March 2020. As of 14 December 2020, there have been more than 74 million confirmed cases and 1.6 million confirmed deaths worldwide (WHO 2020a). Early epidemiologic data show that approximately 12% of SARS-CoV-2-positive subjects require hospitalisation, and of these, nearly 24% may need treatment in the intensive care unit (Guan et al 2020, Centers for Disease Control and Prevention, 2020).

More severe COVID-19 typically presents as viral pneumonia and systemic disease impacting multiple organ systems. Older age, male gender, and comorbidities such as cardiovascular disease, respiratory disease, or type 2 diabetes, are risk factors for disease progression, associated complications, and death (Arentz et al 2020; Grasselli et al 2020; Guan et al 2020; Williamson et al 2020). Although the mechanisms behind the increased risk are not yet fully understood, presence of cardiometabolic or other comorbidities with underlying inflammation and endothelial dysfunction, combined with already compromised baseline organ function, increase the susceptibility to further oxidative stress, inflammation and metabolic derangements by COVID-19 (Ayres 2020; Guzik et al 2020; Madjid et al 2020).

Evolution of the pandemic varies across countries, affected in part by different containment strategies ranging from extreme lockdown to relative inaction. As a result, there have been (and continue to be) regional waves of the disease. Globally, governments have acknowledged that an effective vaccine against COVID-19 is the only way to guarantee a safe and sustained exit strategy from repeated lockdowns. The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts, and widespread vaccination is urgently needed.

AZD1222 is one of the available COVID-19 vaccines—based on different platforms—that have been authorised for emergency use or granted conditional approval after showing relevant vaccine efficacy and significant clinical benefit in this patient population (Baden et al 2021; Polack et al 2020; Voysey et al 2020). The AZD1222 vaccine has been approved for emergency supply authorisation by the MHRA based on interim efficacy results in a regimen of two standard doses administered 4-12 weeks apart for adults over 18 years of age . Additionally, the following markets (among others) have granted authorisation for AZD1222: the EMA granted a conditional marketing authorisation for the prevention of COVID-19 in people from 18 years of age; and the WHO granted Emergency Use Listing for the use of the vaccine in individuals 18 years of age and older, including those aged 65 years and above.

In order to change the course of the pandemic broad access to a variety of vaccines offering protection against SARS-CoV-2 is crucial. Thus, the availability of vaccines with sub-freezing shipping and storage requirements, as well as a lower price, will provide better options for countries to ensure proper and easy vaccine access to a wider population, regardless of economic status and regional needs.

1.3.1 Rationale for the Development of AZD1222

World-wide efforts to develop effective vaccines against SARS-COV-2 are underway; a number of candidates are currently in clinical development (Liu et al 2020). Temporary authorisation for the use of Pfizer/BioNTech's COVID-19 mRNA Vaccine BNT162b2 (which, like AZD1222, encodes for the S glycoprotein) was first granted in the UK; other countries have followed suit. Given the extent and continued rapid pace of infection, the severity of this pandemic's medical and socioeconomic impacts, and the supply challenges associated with a global vaccination program, multiple vaccines are needed. The COVID-19 Vaccine AstraZeneca (AZD1222) has been developed to address this public health need.

The S protein subunits were selected as candidate antigens for vaccine development. They are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells (Li et al 2016). The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The S glycoprotein plays a role in receptor binding and membrane fusion representing a main target for vaccine

and antiviral development. The spike protein is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the SARS-CoV-2 virion.

The nucleic acid sequence coding for the recombinant S protein expressed by AZD1222 was incorporated into the adenoviral vector ChAdOx1, and no other components of SARS CoV-2 are part of AZD1222. The S glycoprotein transgene and gene product are not toxic or pathogenic and do not confer advantage to the viral vector in terms of survival or recombination (see Module 1.6, Section 2). The vector is driven by the human cytomegalovirus major immediate early promoter that includes intron A with a leading tissue plasminogen activator signal sequence at the N terminus. AZD1222 expresses a codon-optimised coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947.

Chimpanzee adenoviruses have a very limited host range, are unable to infect plant cells, are not known to be pathogenic to any other animal species, and do not integrate into the genome (Lee et al, 2017, Morris et al, 2017). These properties are not modified in AZD1222, which is also replication deficient. The antigen expression cassette does not alter the transmission route or host range of the ChAdOx1 viral vector. If a chimpanzee is accidentally exposed, a very low dose of a replication-deficient virus is unlikely to cause symptoms and the vaccine and the expressed gene product would be broken down and processed naturally by the immune system (see Module 1.6.2, Section IIC2i(ii)).

Selection of the ChAdOx1 platform afforded an opportunity to rapidly produce a candidate COVID-19 vaccine for clinical studies, relying on information about immune response, dose response, and safety obtained from experience with other candidate vaccine constructs under development. In addition, the platform lends itself to rapid production of large quantities of vaccine at a relatively low cost, and the product can be formulated for storage at 2°C to 8°C, simplifying cold-chain requirements.

Non-clinical data

AZD1222 has been shown to be immunogenic in BALB/c and CD-1 mice, ferrets, NHP, and pig models, and showed evidence of protection, with no VAED, in a study of post-vaccination SARS-CoV-2 challenge in rhesus macaques (see Module 2.4, Section 2).

Two toxicology studies with AZD1222 have been completed to date with no adverse findings; a preliminary developmental and reproductive toxicity study in mice (see Study 490838) and a cardiovascular and respiratory safety study in mice (see Study 617078). A repeat-dose GLP toxicity study with AZD1222 in mice has been conducted; results showed no adverse findings; (see Study 513351 w/o recovery pathology). A main developmental and reproductive toxicity study in mice with AZD1222 is ongoing (see Study 490843). In addition, non-clinical

toxicology findings with the ChAdOx1 MERS-CoV vaccine expressing the full-length S protein in mice are considered of direct relevance to the non-clinical safety profile of AZD1222. Results from toxicology studies on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) are also considered to be of significance. In the ChAdOx1 MERS-CoV study (see Study QS18DL), the spectrum and severity of the changes were consistent with the administration of an antigenic substance such as ChAdOx1 MERS, and considered to be non-adverse. Results from toxicology studies in mice on similar replication-defective ChAd vaccines (ChAd OX1 NP+M1 and AdCh63 MSP-1) showed similar findings and were well tolerated with no adverse effects (see Studies XMM003 and UNO0013).

In a biodistribution study of AdCh63 MSP-1 in mice, using co-culture expansion for detection of live virus from samples, followed by RT-PCR, dissemination was confined to the site of injection and draining lymph nodes, with no evidence of replication of the virus (see Study RMBIODIST-001). Recently, an ongoing biodistribution study (see Study 0841MV38.001) of IM ChAdOx1 HBV in mice indicated, based on interim data using a more sensitive method, qPCR, low levels of detection of ChAdOx1. Low copy numbers were found in a range of organs (spleen, brain, heart, kidney, liver, lung, lymph node, testes, ovary) at levels 1000 to 100000 fold less than at the injection site (skeletal muscle). There have been no adverse findings in repeat dose toxicity or reproductive toxicity studies associated with this observation.

Because AZD1222 is replication-incompetent in human cells (see Section 3), and because data are available on biodistribution and clinical shedding of other replication-incompetent chimpanzee adenoviral-vectored vaccines, no studies of AZD1222 biodistribution or clinical shedding have been performed, and none are planned.

Shedding on the skin and in urine has been evaluated in participants from 2 clinical studies of the ChAd vaccine AdCh63 ME-TRAP. Following intradermal and IM administration, there was no detectable ChAd vaccine in urine, and while the ChAd could be detected in skin swabs at the site of injection, the amount of viral material recovered was very low compared to the dose given (0.00000549% loss of vaccine dose (2×10^{11} vp) to zero detectable virus (see Module 1.6.2, Section IIC2i(iii)). In the mice study of ChAdOx1 HBV referred to above, shedding was assessed in faeces and urine; preliminary data suggest no shedding occurred in those matrices.

1.4 Clinical Development Programme

1.4.1 Programme Overview

The clinical development programme investigating the efficacy, safety, and immunogenicity of AZD1222 for the prevention of COVID-19 in adults consists of 9 ongoing studies.

including 5 University of Oxford-sponsored studies, 3 Applicant-sponsored studies, and 1 study sponsored by the Serum Institute of India/Indian Council of Medical Research.

The AZD1222 vaccine has been approved for emergency supply authorisation by the MHRA based on interim efficacy results in a regimen of two standard doses administered 4-12 weeks apart for adults over 18 years of age. Additionally, the AZD1222 vaccine was granted a conditional marketing authorisation from the EMA for the prevention of COVID-19 in people from 18 years of age.

Data presented in this submission are pooled from the first 4 studies to enrol participants in this clinical programme: COV001 (Phase I/II); COV002 (Phase II/III); COV003 (Phase II/III) and COV005 (Phase I/II). These studies were all sponsored by University of Oxford and have similar endpoints and methods of surveillance that support the pooling of data. An overview of the University of Oxford studies that form the basis of clinical efficacy, safety, and immunogenicity evidence summarised in this document is provided in Table 1. For details, see Module 5.2 and the study protocols in Module 5.3.5.1 (COV001 CSP version 12.0, COV002 CSP version 15.0, COV003 CSP version 8.0, and COV005 CSP version 4.1).

An overview of the additional studies in this program is provided in Table 2.

Table 1 Studies Included in the Pooled Analysis Presented in the Clinical Overview

Study Identifiers Region	**COV001 (NCT04324606) UK**	**COV002 (NCT04400838) UK**	**COV003 (ISRCTN89951424) Brazil**	**COV005 NCT04444674 South Africa**
Sponsor	University of Oxford	University of Oxford	University of Oxford	University of Oxford
Start Date / Status	April 2020 / Ongoing	May 2020 / Ongoing	June 2020 / Ongoing	June 2020 / Ongoing
Phase	I/II	II/III	III	I/II
Design	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Double blind, randomised, controlled
Planned (actual) number of participants	~1090 (actual: 1077)	~~12390 (actual 10812)	~10300 (actual 10414)	~2070 (actual 2125)
Characteristics of participants included in the pooled analyses	18-55 yr, healthy	≥ 18 yr, healthy	≥ 18 yr, healthy	≥ 18-65 yr, healthy
Number of doses (IM route)	1 or 2 (based on study group)	1 or 2 (based on study group)	2	2
AZD1222 dose levels [a]	SD: 5×10^{10} vp LD: 2.5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp[b]
Control	MenACWY	MenACWY	MenACWY (first dose) Saline Placebo (second dose)	Saline Placebo
Case Detection	Passive	Passive and active (weekly swabbing, SARS-CoV-2 PCR)	Passive	Passive and active (by-visit nasal swabs and/or saliva collection, SARS CoV-2 PCR)
Planned duration of Follow-up	364 days after the last dose	364 days after the last dose	364 days after the last dose	364 days after the first dose

[a] AstraZeneca assay of reference, see Section 1.4.2 for additional details
[b] Estimated administered dose, see Section 2 for additional information
HIV = human immunodeficiency virus; IM = intramuscular; vp = viral particles; wk = weeks; yr = years; MenACWY = meningococcal group a, c, w-135, and y conjugate vaccine.

Table 2 Additional Studies in the Clinical Programme[a]

Study Identifiers Region	**COV004 (PACTR202005681895696) Kenya**	**D8110C00001 (NCT04516746 EudraCT number 2020-001228-32) United States, Chile, Peru**	**D8111C00001 Russia**	**D8111C00002 (NCT04568031) Japan**	**ICMR/SII-COVISHIELD India**
Sponsor	University of Oxford	AstraZeneca	AstraZeneca	AstraZeneca	ICMR/SIIPL
Start Date/Status	October 2020 / Ongoing	August 2020 / Ongoing	On Hold[b]	August 2020 / Ongoing	August 2020 / Ongoing
Phase	Ib/II	III	III	I/II	II/III
Design	participant-blind, randomised, controlled	double-blind, randomised, controlled	Open label	double-blind, randomised, controlled	observer-blind, randomised, controlled
Planned number of participants	~400	~30000	~100	~256	~1600
Participant characteristics	≥ 18 yr, healthy	≥ 18 yr, healthy or with medically-stable chronic disease	≥ 18 yr, healthy	≥ 18 yr, healthy	≥ 18 yr, healthy
Number of doses (IM route)	1	2	1	2	2
AZD1222 dose levels [c]	SD: 5×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp OR COVISHIELD: 5×10^{10} vp
Control	Rabies vaccine	Saline Placebo	None	Saline Placebo	Placebo (Vaccine vehicle)
Planned dose interval	-	4 wk	-	4 wk	4 wk
Case detection	Passive	Passive and active (weekly contacts)	Not applicable	Passive	Passive

Study Identifiers Region	**COV004 (PACTR202005681895696) Kenya**	**D8110C00001 (NCT04516746 EudraCT number 2020-001228-32) United States, Chile, Peru**	**D8111C00001 Russia**	**D8111C00002 (NCT04568031) Japan**	**ICMR/SII-COVISHIELD India**
Planned duration of Follow-up	~365 days after the dose	~730 days after the first dose	~180 days after the dose	~365 days after the first dose	~180 days after the last dose

[a] None of these studies contribute data to this application; therefore they are not listed in CTD Module 5.2

[b] Vaccinations not started; safety data in review by Russian Ministry of Health

[c] AstraZeneca assay of reference, see Section 1.4.2 for additional details

ICMR = Indian Council on Medical Research; IM = intramuscular; vp = viral particles; wk = weeks; yr = years; MenACWY meningococcal group a, c, w-135, and y conjugate vaccine; SII = Serum Institute of India Private Limited/delete this default footnote as required.

1.4.2 Deviations from Initial Planned Study Design, for Studies Included in the Pooled Analyses

Due to a difference in concentration determination between 2 analytical methods, a subset of participants in COV002 who were to receive 5×10^{10} vp (designated as SD) per protocol actually received 2.2×10^{10} vp (designated as LD). Participants who received LDSD were included in the pooled analyses of efficacy and immunogenicity (Voysey et al 2020). A small number of participants in the COV005 study were also administered an LD due to variability in the contract manufacturing organisation used to quantify viral particles in DP. Data from participants in the COV005 study were only included in the pooled analysis of safety. These discrepancies occurred early in the course of the clinical programme; analytical methodologies have since been further validated to reach a level of full confidence in concentration determination. Additional details regarding the LD administration in COV002 and COV005 are provided in Section 2.

The initial intent of this programme was to implement a one dose only immunization schedule. When it became apparent, following review of immunogenicity data from COV001, that a second dose provided increased immunogenicity, a decision was made to more extensively evaluate a 2 dose schedule. As a result, and in the context of logistical constraints related to the rapid conditions in which this clinical programme and scale-up manufacturing were initiated in parallel, delays occurred in clinical trial material availability for second dose vaccinations in all 4 studies, mainly affecting the UK studies COV001 and COV002. Because of these delays, the interval between doses 1 and 2 (originally intended to range from 4 to 12 weeks) actually ranged from 3 to 26 weeks (data on file). Results of preliminary exploratory analysis of the effect of dose interval on efficacy are discussed in Section 4.2.9.1.

1.5 Compliance with Regulatory Guidance and Good Clinical Practice

1.5.1 Consultations with Regulatory Authorities Relevant to this Application

Table 3 presents a summary of previous consultations with MHRA and EMA.

Table 3 Summary of consultations with regulatory authorities

Topic(s)	Agency Advice
Pre-submission meetings: 31 July 2020 (EMA); 04 August 2020 (MHRA)	
Strategy to analyse pooled data from University of Oxford-sponsored studies COV001, COV002, COV003 and COV005. Statistical Analysis Plan	• Open to proposed strategy • Applicant advised to seek Scientific Advice to further inform approach
Scientific advice: 04 September 2020 (MHRA; 2369/AZD1222 COVID-19 vaccine); 11 September 2020 (EMA; EMEA/H/SA/4655/1/2020/II)	

Topic(s)	Agency Advice
Revised Statistical analysis plan	EMA: • Applicant advised to address differences in study design that have potential implications for the pooling process • Recommended lower bound of CI surrounding vaccine efficacy be ≥20% or even ≥30% • Recommended point estimate of VE be well above 50% MHRA: • Supported pooling strategy, plans for a regulatory decision, and statistical requirements for vaccine efficacy
Agency meetings with MHRA and EMA on 6 and 7 October 2020	
Revised Statistical analysis plan	• Acknowledged Applicant's incorporation of lower bound of vaccine efficacy CI >20%; expressed preference for 30% • Acknowledge Applicant's rationale for alpha levels as clear and consistent with controlling type 1 error • Agreed with rationale for approach to alpha spending • Acknowledged potential need to adjust testing strategy if cases not accrued in a timely manner. • Advised Applicant to present refined SAP for additional Scientific Advice
Scientific Advice: 28 October 2020 (EMA; EMEA/H/SA/4655/1/FU/1/2020/II)	
Revised statistical analysis plan	• Alpha spending approach for testing strategy is acceptable if finalized before any interim analysis is performed • Accepted approach to include both SDSD and LDSD regimens in pooled datasets for interim and primary analyses of the primary efficacy endpoint to support a 2 dose regimen, provided immunogenicity data similar across age dose regimens and regions • Applicant advised to conduct analyses at a time when regulatory requirements could be maximized • Applicant advised to reduce number of planned analyses • Agreed that revised approach could form the basis for a regulatory decision
Meetings: 12 November 2020 (MHRA); 18 November 2020 (EMA)	
Final Statistical Analysis Plan	• MHRA and EMA agree that: ◦ final SAP reflects prior advice ◦ final SAP is consistent with Agency expectations of the data

Topic(s)	Agency Advice
Rolling submission plan to provide statistical outputs in 4 submission packages	• Advised applicant to include analysis of serostatus at baseline in subpopulation analysis • MHRA and EMA informed applicant that clinical summaries (Sections 2.7.3 and 2.7.4) not needed for initial review. • MHRA informed applicant that benefit risk assessment needed in place of overview and summaries • EMA advised that Clinical Overview (Section 2.5) required prior to an approval • Rolling submission plan updated to incorporate Agency feedback ° Clinical Package 1: high-level results; ° Clinical Package 2: full population; ° Clinical Package 3: subgroups (by age, country, comorbidity, and serostatus at baseline); and ° Clinical Package 4: Immunogenicity, clinical overview, RMP, QRD
Other Topics	
Older Adults (EMA)	• Pooled primary analysis should include participants ≥ 65 years of age (25% of total enrolment preferred). • If 25% target not reached, additional information on efficacy in older adults may be required later. • Applicant to report participants ≥ 65 years in the pooled analysis, with a descriptive tabulation of cases in the AZD1222 and control groups
Safety	MHRA and EMA: • One month post-second dose safety date to be available for a substantial number of participants so it can be reviewed during the assessment period. EMA: • Applicant to provide safety tabulations by: ° dose and dose interval, ° age subgroup, ° receipt of paracetamol within the period in which solicited AEs were captured.
Paediatrics • Designs of studies included in the PIP • Proposal to defer these studies with completion date of March 2023	• PIP opinion received 05 January 2021.

1.5.2 Compliance with Good Clinical Practice

All studies in the clinical study programme have procedures in place to comply with GCP, as documented by the ICH and applicable health authorities' regulations and guidelines.

2 OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutic studies with different formulations were not conducted as AZD1222 is only intended for IM use.

The bioanalytical methods used to assess serostatus at baseline and immunogenicity (ie, humoral and cellular immune responses) in the clinical development programme were precise and accurate, and the assay validation or qualification characteristics were acceptable for all applications. While methods used in early clinical development are referred to in this document, the methods discussed in Sections 3.4 and 4.2.8 are qualified and/or validated.

The commercial AZD1222 DP is formulated to ensure stability and provide convenience for dose administration. AZD1222 DP is a sterile preservative-free liquid dosage form, presented in a multi-dose vial at 1×10^{11} vp/mL intended for IM administration. Each dose is prepared by withdrawing 0.5 mL from a vial of AZD1222 in a sterile syringe.

Unopened vials must be stored at 2°C to 8°C. After opening, vials must be discarded within 6 hours (if stored at room temperature, ie, 30°C) or within 48 hours (if stored at 2°C to 8°C).

The manufacturing process evolved during the development programme (Table 4). AZD1222 clinical trial material was sourced from: 1) CBF at the University of Oxford (Process 1) for Study COV001; 2) Advent (Process 2) for Studies COV002, COV003, and COV005; and 3) Cobra/Symbiosis Biologics (Process 3) for Studies COV001, COV002, COV003, and COV005. The intended commercial DP is prepared using Process 4. The DP development was supported by analytical comparability.

For Studies COV001, COV002, COV003, and COV005, the DP is supplied as a sterile solution in a single or multiple-dose vial. For details on the materials and formulations (including dosage form, concentration, and label-claim volume) used in each clinical study, and for the intended commercial material, see Module 3.2, Section P.2.2.

A quality control analysis of DP used in the COV002 study revealed discrepancies between two methods used by contract manufacturer and University of Oxford (CBF) to quantify viral particles, namely qPCR and spectrophotometry, resulting in approximately 2.3-fold difference in determined vp. In consultation with the MHRA, it was agreed to dose based on viral particle content as ascertained by the spectrophotometric method in the COV002 study to maintain consistency with the COV001 study and ensure participants were not given a higher than planned dose for safety considerations. This resulted in selection of a dose of 5×10^{10} vp by spectrophotometer (2.2×10^{10} vp by qPCR) from lot K.0007. However, a low reactogenicity among vaccinated participants was observed and further investigations identified an unexpected interference of an excipient, polysorbate 80 (PS80) with the spectrophotometry assay. Polysorbate 80 amplifies the absorbance which, if not corrected, can

lead to overestimation of the viral particle concentration. This overestimation led to the over-dilution of the DP concentration in the original vial resulting in the delivery of approximately half (45%) the intended dose administered to a subset of participants in the COV002 study.

In the COV005 study, 44 participants were also administered a lower dose of AZD1222 from the DP lot K.0011. This was a result of an overestimation of the vp content in the DP as measured by qPCR by the contract manufacturer, as a result of known variability in the assay. Remeasurement of the vp content in the DP using commercially optimized qPCR and digital droplet PCR methods by the Applicant yielded values that were lower than that estimated by the contract manufacturer. The consistency between the results obtained via these two different methods used by the Applicant provided a more accurate and reliable measure of the vp content in the DP. It was concluded that the qPCR vp content for K.0011 as ascertained by the contract manufacturer was artificially high. Due to this initial overestimation of the vp content, the first few participants were administered a lower volume of injection to achieve the standard dose. In light of the values obtained during the remeasurement, the dose volume was adjusted to achieve a comparable standard dose to the other studies after consultation with the South African Regulatory authorities.

Comparative analyses revealed that there were no meaningful differences between the SD using Advent DP when the volume was adjusted, and the Cobra/Symbiosis DP, as measured by vp, infectious particles per dose, and the vp: infectious particles (P:I) ratio between the SD delivered using DP manufactured at different sites and used in the COV001, COV002, COV003, and COV005 studies using necessary volume adjustments. A suite of assays have now been developed for determination of dose strength (which confirmed the LD and SD dosing), and future batches are all released with a specification dose of 3.5 to 6.5 $\times$ 10^{10} vp. For additional details, see the Low Dose Delivery of AZD1222 in Study COV002 and Study COV005 document (see Appendix A, Section 8.1).

Table 4 Drug Product Development Summary

Category	Process 1 (clinical)	Process 2 (clinical)	Process 3 (clinical)	Process 4 (intended commercial)		
Study	COV001	COV002, COV003, COV005	COV001, COV002, COV003, COV005	---	---	---
Dosage form	Frozen liquid	Frozen liquid	Liquid	Liquid		
	Single-dose	Multiple-dose (2)	Multiple-dose (10)	Multiple-dose (10)		Multiple-dose (8)
AZD1222 concentration	1.3×10^{11} vp/mL[a]	1.7×10^{11} vp/mL[a]	1×10^{11} vp/mL	1×10^{11} vp/mL		
Formulation	10 mM histidine, 35 mM NaCl, 1 mM $MgCl_2$, 0.1 mM disodium edetate, 7.5% (w/v) sucrose, 0.5% (v/v) ethanol, 0.1% (w/v) PS-80, pH 6.6 [b]		10 mM histidine, 35 mM NaCl, 1 mM $MgCl_2$, 0.1 mM EDTA, 7.5% (w/v) sucrose, 0.5% (v/v) ethanol, 0.1% (v/v) PS-80, pH 6.6[b]	10 mM histidine/histidine-HCl, 35 mM NaCl, 1 mM $MgCl_2$, 0.1 mM disodium edetate, 7.5% (w/v) sucrose, 0.5% (v/v) ethanol, 0.1% (w/v) PS-80, pH 6.6		
Label-claim volume	0.35 or 0.485 mL[c]	1 mL	5 mL	5 mL	5 mL	4 mL
Vial	2R borosilicate clear and colorless (Adelphi)	3 mL borosilicate clear and colorless (Nuova Ompi-Stevanato)	10R borosilicate clear and colorless (Schott)	10R borosilicate clear and colorless (Schott, Soffieria Bertolini, Nipro, Gerresheimer)	6 mL borosilicate clear and colorless (Thüringer)	5 mL borosilicate clear and colorless (Gerresheimer)
Stopper	13 mm FM157 (Datwyler)	13 mm S2-F451 (West)	20 mm 4023/50 FluroTec (West)	20 mm 4023/50 FluroTec (West) 20 mm FM259 OmniFlex (Datwyler) 20 mm D21-7S FluroTec (Daikyo)	13 mm 4432/50 FluroTec (West)	13 mm 4432/50 FluroTec (West)

Table 4 Drug Product Development Summary

Category	Process 1 (clinical)	Process 2 (clinical)	Process 3 (clinical)	Process 4 (intended commercial)		
Seal	13 mm aluminium	13 mm aluminium	20 mm aluminium	20 mm aluminium	13 mm aluminium	13 mm aluminium

PS-80 = polysorbate 80; vp = viral particles

[a] Diluted at clinic to target 1×10^{11} vp/mL
[b] By pH titration using HCl
[c] Two lots were manufactured with two different label-claim volumes.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

Immunogenicity data from the interim pooled analysis (DCO1 04 November 2020) have previously been submitted. Updated immunogenicity data from the primary pooled analysis (DCO2 07 December 2020) is presented and summarised in this section (for complete data and analysis see SCP, Module 5.3.5.3). All data outputs from this primary pooled analysis are provided in Module 5.3.5.3. Additional data outputs for exploratory analyses of immunogenicity are provided in Module 5.3.5.3 of this submission. As the clinical studies are currently ongoing, clinical study reports are not available, and analyses have not been performed by study.

Of note, due to a programming error, 1522 baseline records, 1472 Day 28 post-baseline records, and 1474 Day 28 post-dose 2 records for both S and RBD were excluded from the interim (04 November 2020) analysis. This resulted in 800 participants being excluded from the immunogenicity analysis set, all of whom were in the COV002 and COV003 studies (note that many participants with excluded data were already included in the immunogenicity analysis set due to having post-baseline data from at least one other assay). The previously excluded data, including new data as a result of a later data cut, are included in the DCO2 analysis set.

Overall, all key messages from the primary analysis (DCO2) were consistent with the data submitted during the interim analysis (DCO1).

3.1 Chimpanzee Adenoviral Vectors

Chimpanzee adenoviruses have been developed as viral vectors following concerns that pre-existing immunity to human adenoviral serotypes could limit future widespread use of these viruses as vaccine platforms. Chimpanzee adenoviruses and human adenoviruses are not phylogenetically distinguishable and fall into the same 8 species (A, B1, B2, and C to G). ChAd63, ChAdOx1 and ChAdOx2 are, like many chimpanzee adenoviruses isolated to date, members of species E, which contains only one human virus (HAdV-4).

Chimpanzee adenoviruses are not known to cause pathological illness in humans, and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US (Tatsis et al 2007). In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titre neutralising antibodies to AdHu5, whilst only 4% had high-titre neutralising antibodies to ChAd63. Immunity to both vectors increases with increasing age (Dudareva et al 2009).

Cellular immunogenicity of recombinant E1 E3-deleted ChAdOx1, used to assemble AZD1222, is comparable to that of other species E derived chimpanzee adenovirus vectors

including ChAd63, the first chimpanzee adenovirus vector to enter clinical trials in humans (Dicks et al 2012).

3.1.1 Anti-vector Immunity

Pre-existing immunity to ChAdOx1vectors has been shown to be low and not cross-reactive with other ChAd vectors, such as ChAd63 (Dicks et al 2012). The Phase I/II study to evaluate safety and immunogenicity of AZD1222, COV001, demonstrated that anti-vector (ie, anti-ChAdOx1) responses are induced after a single dose of AZD1222, with similar titres elicited after either a first LD or a first SD. These anti-vector responses do not increase following a second dose (Folegatti et al 2020b, Barrett et al 2020). Anti-ChAdOx1 neutralising antibody titres at the time of the second dose did not correlate with spike-specific antibody response following the second vaccination measured by standardised ELISA 28 days after the second dose in adults 18 to 55 years of age. Additionally, anti-ChAdOx1 neutralising antibody titres did not correlate with Spike-specific T cell response measured by IFNγ ELISpot 28 days after the participants received SDSD regimens (Barrett et al 2020).

3.2 Mechanism of Action

AZD1222 is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, this S glycoprotein is expressed locally and stimulates a humoral and cellular immune response.

The ChAdOx1 (AdvY25) viral vector is replication-deficient as the essential E1 gene region has been deleted. Thus, the virus can only propagate in cells expressing E1 functions and is unable to replicate within vaccinated animals or humans.

The ChAdOx1 platform has been or is currently being used in clinical studies with immunogens from multiple pathogens such as influenza, tuberculosis, malaria, chikungunya, Zika, MERS-CoV, and capsular group B meningococcus. ChAdOx1 vectors induce humoral, mucosal, and cell-mediated immune responses (Hassan et al 2020). Single dose administration of AZD1222 induces high levels of antibody responses (including IgG, IgM, and IgA) 14 to 28 days post administration, including neutralising antibodies in 91% to 100% of participants, indicating immune responses that may confer protection is afforded in the first two weeks after AZD1222 administration (Folegatti et al 2020b). Geometric mean titres of nAbs were not statistically different between age cohorts when examined in a Phase II/III study (Ramasamy et al 2020). By 14 days after the second dose of AZD1222, > 99% of study participants receiving two doses, including those aged > 70 years, had a seroresponse. Neutralising antibody responses correlated strongly with binding antibody responses, as measured by a multiplexed ECL-based assay (Folegatti et al 2020a).

A second dose of AZD1222 increases both the magnitude and avidity of antigen-specific IgG generated (Barrett et al 2020). The generation of S-specific antibodies by AZD1222 has been shown to be highly polarized toward the production of IgG1/IgG3, with low levels of IgG2/IgG4, and is in agreement with previously published reports describing the induction of Th1-type human IgG subclasses following adenoviral vaccination (Barrett et al 2020, Barouch et al 2018). Moreover, AZD1222 elicits multiple antibody effector functions, which appear to be important for rapid clearance and may contribute to recovery after SARS-CoV-2 infection (Atyeo et al 2020).

In addition to the generation of humoral responses, including nAbs responsible for direct antagonism of SARS-CoV-2, AZD1222 induces cell-mediated immune responses. Assessment by ICS demonstrated that these responses include CD8 T cells with direct effector function (responsible for destroying virus-infected cells, preventing further spread of the virus after infection) as well as robust induction of Th1 responses, which support B cell function for the production of antibodies and are critical in maintenance of T cell responses (Ewer et al 2020).

3.3 Dose and Regimen Selection

The dose regimens chosen for the studies included in the pooled analysis were selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts and with other similar adenovirus vectored vaccines (eg, ChAd63), as well as emerging data from the two-dose regimen utilized in the COV001 study to examine the safety and immunogenicity of AZD1222. The data described in this section references published studies that use smaller group sizes and in some cases different modalities (ie, standardised rather than validated or qualified) for the assessment of immunogenicity. Humoral immunogenicity, as analysed in the Immunogenicity Analysis Set of the pooled analysis, is discussed in Section 4.2.8.

A Phase I open label dose-escalation study (NCT03399578) using a ChAdOx1-vectored vaccine expressing the full-length S protein from a related betacoronavirus, MERS-CoV, evaluated three dose levels (5×10^9 vp, 2.5×10^{10} vp, and 5×10^{10} vp) (Folegatti et al 2020a). After a single dose, all dose levels were well tolerated, and IgG responses increased across all groups, peaking approximately 28 days post vaccination. Responses were highest in the 5×10^{10} vp dose level, where all participants seroconverted by 28 days post vaccination. Neutralising antibodies were noted in the 5×10^{10} vp dose level with no significant increase above baseline seen in the lower dose levels. Additionally, T cell responses to the Spike immunogen of MERS-CoV were seen in all dose levels, with the highest responses observed in the highest dose level. These data are supported by platform data with ChAdOx1 vectors containing alternative immunogens, suggesting a 5×10^{10} vp dose is well tolerated and immunogenic (Dicks et al 2012; Dudareva et al 2009; Folegatti et al 2019).

Candidate vaccines using adenoviral vectors have been utilized in heterologous vaccination regimens (employing other adenovirus serotypes, alternative viral platforms, or nucleic acid) to improve the quantity and quality of immune responses. However, while heterologous vaccine regimens are well established to increase the robustness of immune responses to adenovirus vectors, an adenovirus type 5 Ebola vaccine has previously shown enhancement of both cellular and humoral immunity after a homologous second dose, with a second dose increasing antibody geometric mean titres approximately 9-fold above the levels seen after a prime only (Li et al 2017). Additionally, an approved vaccine for the prevention of Ebola virus utilizes a heterologous prime-boost strategy with a first dose of 5×10^{10} adenovirus serotype 26 containing the Ebola virus Zaire glycoprotein (Ad26.ZEBOV) followed approximately 8 weeks later by a 1×10^{8} dose Modified Vaccinia Ankara expressing multiple glycoproteins from viruses known to cause haemorrhagic fever (MVA-BN-Filo) (Zabdeno EPAR 2020).

In Study COV001, 10 participants received a second dose of AZD1222 four weeks after the first dose. A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a second dose augmenting neutralising antibody titres. Notable increases in antibody levels to the S protein and increases to the RBD were observed while S-specific T cell responses peaked on Day 14. Increases in antibody levels following the second dose were also observed with both live virus neutralisation and pseudo-neutralisation assays. Neutralising antibody responses against SARS-CoV-2 were detected in 91% of participants after a single dose when measured in MNA_{80} and in 100% of participants when measured in $PRNT_{50}$. After a booster dose, all participants had neutralising activity, and neutralising antibody responses correlated strongly with antibody levels ($R^2 = 0.67$ by Marburg VN; $p < 0.001$) (Folegatti et al 2020b). These data were confirmed in larger numbers of study participants by adding a second dose of SD or second dose of LD (Barrett et al 2020)

AZD1222 was evaluated at two dose levels in older adults in Study COV002. After a single LD or SD, anti-S IgG and anti-RBD IgG responses trended lower in participants above the age of 55 years (Ramasamy et al 2020). However these responses were not significantly different from the responses in younger participants. After a second dose of either LD or SD, no significant differences in antigen-specific antibody titres were seen across two-dose groups, regardless of age, although older participants and participants receiving two LDs trended slightly lower and group sizes analysed were small. While some adenovirus vaccines have shown decreasing immunogenicity with increased age (Zhu et al 2020), the robust induction of humoral responses observed with AZD1222 are consistent with platform ChAdOx1-vectored vaccine data, including with influenza antigens that elicit immune responses in adults older than 50 years (Coughlan et al 2018).

The proposed vaccination course for studies COV001, COV002, COV003, and COV005 consisted of two separate IM doses of 5×10^{10} vp AZD1222 each, with the second identical

dose planned at approximately 4 to 12 weeks after the first dose. This two-dose regimen was based upon accumulated evidence from at least four animal species (ie, mouse, ferret, pig, and NHP) and multiple clinical trials (adenovirus type 5 Ebola vaccine trial [Li et al 2017] as well as the two- dose data from Study COV001 [Barrett et al 2020, Folegatti et al 2020b]).

Administering a second dose of AZD1222 at an approximately 4- to 12-week interval, particularly during a pandemic, is operationally appealing, if protection is provided by the first dose, allowing for a flexible interval between the first and second dose. The potential to delay administration of the second dose up to three months may allow rapid induction of immunity in a large population, if coverage with a first dose is prioritized over rapid administration of the second dose. Indeed, available evidence from the pooled efficacy analysis showed that protection was provided after the first dose, approximately 3 weeks after vaccination, before the second dose is administered (Section 4.2.2.2 and Section 4.2.9.2).

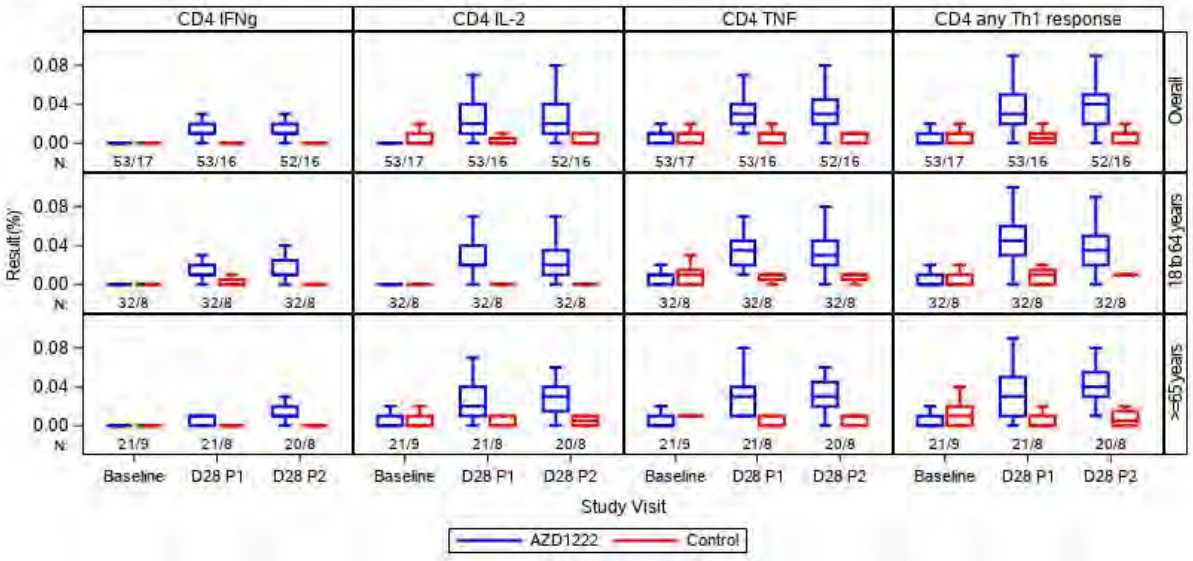
3.4 Cell-mediated Immunity

Assessment of cell-mediated immunity is important for the assessment of safety (ie, Th1/Th2 polarization) as well as the potential vaccine efficacy (McMahan et al 2020). Cell-mediated immunity was assessed by two different methods in the Immunogenicity Analysis Set of the pooled analysis: IFNγ ELISpot was utilised to examine the ability of PBMCs stimulated with overlapping Spike peptide pools to produce IFNγ, and an ICS assay (in an ICS Analysis Set) was utilised to characterise and phenotype the response of PBMCs to overlapped S peptide pools. IFNγ ELISpot responses in the following subgroups were also analysed: age at screening (18 to 64 years, ≥ 65 years), comorbidity at baseline (BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease, or diabetes). PBMCs were isolated from study participants in the UK (COV001 and COV002 studies) as of the data cut-off date (07 December 2020); all data represent the UK subgroup.

S-specific T cell responses (in participants who were seronegative at baseline) as analysed by IFNy+ ELISpot suggest that T cells are induced after a first dose of AZD1222 (with GMR of 607.740, where response indicates SFC/10^6 PBMCs) in the SDSD + LDSD analysis set. These do not rise further after a second dose (GMR = 421.613), consistent with published literature on homologous prime boost (Figure 1, and see Immuno Table 1.7.3.1.1, Module 5.3.5.3; Li et al 2017). ELISpot data similarly suggest that IFNy+ T cell responses (in participants who were seronegative at baseline) were similar in subgroups, with age (18 to 64 years: GMR = 668.092, 561.296; ≥ 65 years: GMR = 572.687, 336.854 after dose 1 and dose 2, respectively; see Table 2 of the SCP, Module 5.3.5.3.) and comorbidity (comorbidity: GMR = 614.622, 375.985; no comorbidity: GMR = 607.131, 431.157) after a first dose, which were not further increased after a second dose (for comorbidity, see Immuno Tables 2.7.3.1.1.a and 2.7.3.1.1.b, Module 5.3.5.3).

ICS was performed on 71 participants (41, age 18 to 64 years; 30, age ≥ 65 years) from the COV001 and COV002 studies; all ICS analysis was performed on participants receiving the SDSD dose level. To assess the lineage, phenotype, and functionality of S-specific T cell responses, PBMCs were stimulated with S1 or S2 peptide pools containing overlapping 15-mer peptides from the full length Spike protein, fixed and stained for markers of Th1 response (IFNγ, IL-2, TNFα) or Th2 response (IL-4 and IL-13). Additionally, lineage (CD3, CD4, CD8) and activation markers were analysed (CD69, CD28, CCR7, CD45RA). At baseline, limited CD4+ cells expressing Th1 cytokines were observed in the control or AZD1222 vaccinated group. At 28 days after first or second dose, induction of Th1 cytokines was noted in the AZD1222 vaccinated participants, with cells expressing IFNγ, IL-2, and/or TNFα. Of note, CD4 populations with polyfunctionality of response were observed (Figure 1; see Supplemental Tables IEMT 194.1 and IEMT 194.2, Module 5.3.5.3). These responses were generally similar between age categories, showing the same functional cytokine profile. Baseline levels of Th2 cytokine responses were minimal in both control and AZD1222 groups, with no increases noted after the first or second dose with AZD1222. These data show a strong induction of an S-specific Th1 polarised response after AZD1222 vaccination.

Figure 1 Th1 Cytokine Expression in SARS-CoV-2 S1 stimulated PBMCs



CD4 IFNg= CD+ IFNγ+; CD4 IL-2= CD4+ IL-2+, CD4 TNF= CD4+ TNFα+; CD4 any Th1 response= CD4+ with any of IFNγ+, IL-2+, TNFα+; D28 P1 = Day 28 post first dose; D28 P2 = Day 28 post second dose.
Source: Supplemental Figure IEMT 194.1.1.1, Module 5.3.5.3.

4 OVERVIEW OF EFFICACY

4.1 Introduction

Efficacy data from the interim pooled efficacy analysis (DCO1, and based on data studies COV002 [Phase II/III; UK], COV003 [Phase III; Brazil]) have previously been submitted and published (Vaysey et al 2020).The pooled analysis provided in this updated submission includes data from the primary analysis (DC02), which includes data from 4 ongoing blinded, randomised, controlled studies conducted across 3 countries: COV001 (Phase I/II; UK), COV002 (Phase II/III; UK), COV003 (Phase III; Brazil), and COV005 (Phase I/II; South Africa). This DCO2 date allowed the accumulation of sufficient cases for the primary analysis. In addition, vaccination of the general population in the UK started on 08 December 2020; therefore, this day was chosen as DCO2 to ensure study data would not be impacted by participants unblinding in order to receive a publicly available vaccine. This DCO2 also allowed for a median follow-up of > 2 months after the second dose, which is considered important for the analysis of safety.

Evidence of efficacy for AZD1222 at the primary analysis is based on pooled data from Studies COV001, COV002 COV003, and COV005; these studies are included in the pooled analysis for efficacy based on having met the predetermined criteria for being included in the pooled analyses. Evidence of immunogenicity and safety for AZD1222 is based on pooled data from all 4 studies. The pooled analysis approach was discussed with MHRA and EMA, and this feedback informed the final strategy for the analysis. (Section 1.5.1).

The study designs of the 4 University of Oxford-sponsored studies COV001, COV002, COV003, and COV005 are sufficiently consistent to justify pooled analyses; an overview of the study designs is provided in Table 1. The studies were single- or double-blinded, controlled and randomized. The inclusion and exclusion criteria were generally similar across studies. All studies enrolled adults 18 to 55 years of age. In addition, all studies have enrolled older adults in age escalation groups of 56 to 69 years of age and ≥ 70 years of age. Enrolment in the initial Phase I Study COV001 was restricted to healthy adults. The other studies allowed the inclusion of participants with stable underlying health conditions with the exception of severe and/or uncontrolled underlying disease. All studies excluded pregnant and breastfeeding women.

Cohorts that would make interpretation challenging were prespecified as excluded from the pooled analysis dataset in the SAP. These included cohorts that were not randomized and had no concurrent control group. Also, the study groups of HIV infected individuals enrolled into Studies COV002 and COV005 were not included, because they are a specific population that will be analysed separately.

Based on data suggesting equivalent immunogenicity provided by either a low dose or a standard dose 28 days post dose 1 (Ramasamy et al 2020), the decision was taken to pool data from LDSD and SDSD recipients for the primary endpoint determination.

Collection and assessment of data for capture of COVID-19 variables included in the pooled interim analysis were performed in a consistent manner across the studies. All participants had good access to health care, and cases of COVID-19 were detected through a combination of active and passive surveillance systems. A single central, blinded, independent adjudication committee was used by all 4 studies to assess COVID-19 cases from all participants with SARS-CoV-2 virologically confirmed results. Each case was assessed by the adjudication committee and classified according to the WHO severity grading scale (Marshall et al 2020). The adjudicated results were used for the pooled analyses.

Case definitions for the pooled analysis are presented in Table 5. Please note that COVID-19 requiring ICU was not reported for DCO2..

Table 5 Case Definitions for Evaluation of Efficacy

Case	Definition
COVID-19 (Primary) Virologically confirmed[a] symptomatic cases of COVID-19	Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. In addition, all virologically confirmed SARS-Cov-2 events with WHO grade ≥4 will be included regardless of presence of symptoms. All cases were adjudicated.
COVID-19 Hospital Admission	WHO grade ≥ 4[b]
COVID-19 Severe Disease	WHO grade ≥ 6[b]
COVID-19 Requiring ICU	WHO grade ≥ 7[b]
COVID-19 Death	WHO grade = 10[b]
Asymptomatic SARS-CoV-2 infection	Virologically confirmed SARS-CoV-2 infection and no symptom record in data. Confirmed by adjudication committee.

[a] Virologically confirmed from RT-PCR or other nucleic acid amplification test.
[b] WHO clinical progression scale.

4.1.1 Statistical Methods

Statistical methods are summarized in Section 4.1 and detailed in the SAP (see MAA SAP Edition 7, Module 5.3.5.3).

The primary analysis was initiated when 271 COVID-19 cases (SARS-CoV-2 virologically confirmed) that occurred ≥ 15 days post the second dose have been reported in participants who received SD/SD across the AZD1222 and control groups. The analysis includes

participants who received two doses, with the second dose being SD (ie, participants who received LD/SD or SD/SD). For an individual study to be included in the pooled analysis of efficacy, a minimum of 5 primary endpoint defined cases must have been accrued. For COV002, only cases accruing in efficacy study groups were included (groups 4, 6, 9, 10).

The testing strategy for this pooled primary analysis was endorsed after consultation with Regulatory Authorities (Section 1.5.1).

A gamma (-2.5) alpha-spending function was used to control the overall Type 1 Error at 5% for the primary efficacy endpoint across the interim analysis and the subsequent primary analysis. The alpha level calculated from the gamma (-2.5) alpha-spending function was 4.16% using the actual number of cases at the interim (98 cases from participants on SDSD). Whilst alpha was determined based on the 98 cases from participants who received SDSD, the primary analysis was prespecified to include participants who received ether SDSD or LDSD (131 cases). Efficacy was declared at the interim analysis and therefore, multiplicity adjusted confidence intervals were only used for the analyses at the interim. All p-values for the primary analysis are considered nominal given efficacy was already declared.

Multiple analysis sets were used for the pooled analyses. For definitions of each analysis set and exclusions from the pooled analyses, see the SAP (see MAA SAP, Edition 7, Module 5.3.5.3); brief details for each analysis are provided in Table 6.

The primary efficacy analysis was based on the SDSD + LDSD Seronegative for Efficacy analysis set (ie, randomised participants who had received LDSD or SDSD, were seronegative, and had follow up data ≥ 15 days post second dose).

The primary efficacy endpoint was first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention, with at least one of the following symptoms: objective fever (defined as ≥ 37.8°C), cough, shortness of breath, anosmia, or ageusia. In addition, all virologically confirmed SARS-Cov-2 events with WHO Grade ≥4 were included regardless of presence of symptoms. Only cases with both the sampling date of positive PCR test (or other nucleic acid amplification test) and COVID-19 symptom(s) onset date ≥ 15 days post second dose were counted as events.

Vaccine efficacy of AZD1222 versus control, the CI, and p-value were estimated based on Poisson regression with robust variance including the terms of study code, treatment, age group at screening (18 to 55, 56 to 69, and ≥70 years) as covariates, as well as the log of the follow-up time as an offset. The p-values testing null hypotheses against a vaccine efficacy of 20% are presented for analysis of primary endpoint in SDSD + LDSD seronegative for Efficacy Analysis Set, as well as the corresponding SDSD + LDSD seronegative ITT, and SDSD seronegative efficacy analysis populations. For rest of analysis, the p-value testing null

hypotheses against a vaccine efficacy of 0% are presented as previously done. All efficacy analyses used a 95% CI.

For analyses of endpoints where there were few events (ie, in sub-group analysis), the pre-specified Poisson regression with robust variance model failed to converge. As stated in the SAP, in this situation, the exact conditional method for stratified Poisson regression using PROC GENMOD with the exact statement was to be used. Upon further review of the high-level results (see Main Efficacy Tables 1.4.1.1, 1.4.1.3, 1.4.2.1, and 1.4.17.1), it was found when the number of events in the AZD1222 arm is 0 and the number of events in the control arm is ≥ 1, the maximum likelihood estimate for the relative risk is zero with corresponding vaccine efficacy of 100%. However, PROC GENMOD gives a median unbiased estimate instead of the maximum likelihood estimate, and the upper confidence limit of vaccine efficacy cannot be estimated in this extreme situation. Therefore, as a change to the planned analysis, if the number of events in the AZD1222 arm is 0 and the number of events in the control arm is ≥ 1, the vaccine efficacy has been set to the maximum likelihood estimate (100%) and the 1-sided 97.5% CI is presented. However, interpretation of these endpoints will be based primarily on descriptive summaries of the number of events.

To support the primary analysis, Kaplan-Meier curves were presented for the active and control groups based on observed events, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention.

For a complete description of the statistical methods, see Sections 9 (Efficacy) and 11 (Immunogenicity) of the SAP (see MAA SAP, Edition 7, Module 5.3.5.3).

To explore the implications for efficacy and immunogenicity among different populations, including those at high risk of severe COVID-19, the following subgroups were evaluated at this primary analysis and are described in this document:

- Age at screening;
  [redacted] years
- Comorbidity at baseline (at least one comorbidity versus no comorbidity), where comorbidity is BMI ≥ 30 kg/m^2, a cardiovascular disorder, respiratory disease, or diabetes
- Country (UK [Studies COV001 and COV002], Brazil [Study COV003], or South Africa [Study COV005])
- Baseline serostatus, based on SARS-CoV-2 nucleoprotein serostatus

4.2 Efficacy Results

The primary population for analysis was SDSD + LDSD as prespecified in the SAP. It was foreseen to analyse the SDSD cohort as supportive of the primary analysis. Data are

presented for the SDSD + LDSD Seronegative for Efficacy Analysis Set (the primary efficacy population) and the SDSD Seronegative for Efficacy Analysis Set, as described in the pooled analysis SAP. In addition, data are presented for the SDSD Seronegative for Efficacy Analysis Set, for participants with a 4-12 week dosing interval, as this is the recommended dosing regimen. The detailed evaluation of exploratory findings of differential efficacy between regimens is presented in Section 4.2.8.

4.2.1 Participant Population Studied

4.2.1.1 Participant Disposition

Table 6 presents the disposition of participants in the pooled analysis sets for efficacy, safety, and immunogenicity. Figure 2 presents a flow chart for the disposition of participants in the efficacy analysis sets.

Table 6 Disposition of Participants in Pooled Analysis Sets

Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	Control	Total
All participants randomized	As randomized				12280	11977	24257
Safety							
Any Dose for Safety	As treatment received	Pos and Neg and Missing	Any	From Dose 1	12282	11962	24244
Dose1 SD for Safety	As treatment received	Pos and Neg and Missing	SDSD SD single dose SDLD	From Dose 1	10317 (84.0)	10141 (84.8)	20458 (84.4)
Efficacy							
Any Dose for Efficacy	As treatment received	Pos and Neg and Missing	Any	From Dose 1	11794 (96.0)	11776 (98.4)	23570 (97.2)
SDSD + LDSD Seronegative for Efficacy (Primary population)	As treatment received	Seronegative	SDSD LDSD	From 15 days post Dose 2	8597 (70.0)	8581 (71.7)	17178 (70.9)
SDSD + LDSD Seronegative ITT for Efficacy	As randomized	Seronegative	SDSD LDSD	From 15 days post Dose 2	8603 (70.1)	8586 (71.7)	17169 (70.9)
SDSD Seronegative for Efficacy	As treatment received	Seronegative	SDSD	From 15 days post Dose 2	7201 (58.6)	7179 (60.0)	14380 (59.3)
SDSD Seronegative for Efficacy, 4-12 weeks dosing interval	As treatment received	Seronegative	SDSD, 4-12 weeks dosing interval	From 15 days post Dose 2	5849 (47.6)	5763 (48.2)	11612 (47.9)
LDSD Seronegative for Efficacy	As treatment received	Seronegative	LDSD	From 15 days post Dose 2	1396 (11.4)	1402 (11.7)	2798 (11.5)
Dose1 SD Seronegative for Efficacy	As treatment received	Seronegative	SDSD SD single dose SDLD	From 22 days post Dose 1	9335 (76.0)	9312 (77.8)	18647 (76.9)

Table 6 Disposition of Participants in Pooled Analysis Sets

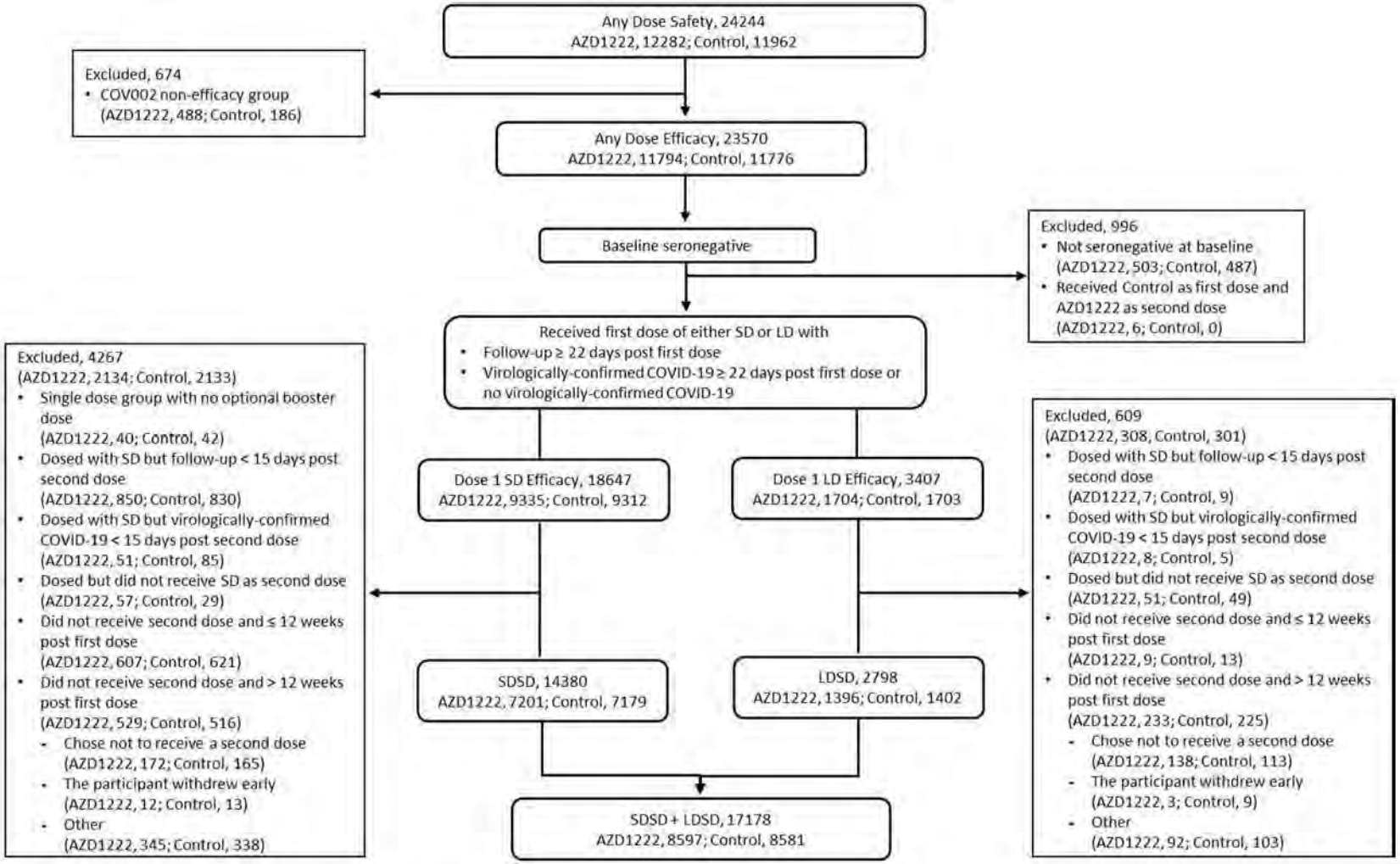
Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	Control	Total
Dose1 LD Seronegative for Efficacy	As treatment received	Seronegative	LDSD LD single dose LDLD	From 22 days post Dose 1	1604 (13.9)	1703 (14.2)	3407 (14.1)
Immunogenicity							
SDSD + LDSD for Immunogenicity	As treatment received	Pos and Neg and Missing	SDSD LDSD	All available timepoints	2135 (17.4)	1577 (13.2)	3712 (15.3)
SDSD for Immunogenicity	As treatment received	Pos and Neg and Missing	SDSD	All available timepoints	1758 (14.3)	1354 (11.3)	3112 (12.8)

LD = low dose; Neg = negative; Pos = positive; SD = standard dose.

Denominator used in the percentage calculation is the number of participants in the Any Dose for Safety Analysis Set.

Source: Main Safety Tables 1.1.1.1; Immuno Table 1.1.1.2, Supplementary Table IEMT 182.1.2.1, Module 5.3.5.3

Figure 2 Disposition of Participants for the Efficacy Analysis Sets (AZD1222 Pooled Analysis)



COVID-19 = coronavirus disease 2019; LD = low dose; SD = standard dose.

Source: Main Safety Tables 1.1.1.1 and 1.1.2.1.

4.2.1.2 Exposure to AZD1222

As of DCO2 (07 December 2020), 12282 participants of the 4 studies included in the application have received at least one dose of AZD1222. Of these participants, 10448 (85.1%) have received 2 doses of AZD1222 (Table 7; see Main Safety Table 1.2.1.1, Module 5.3.5.3).

Overall and in the primary efficacy analysis set, approximately one-third of participants had a dose interval in each of the categories < 6 weeks, 6 to 11 weeks, or ≥ 12 weeks.

The proportion of participants with dose intervals < 6 weeks was lowest in the SDSD + LDSD Seronegative for Efficacy Analysis Set (45.4%), and highest in the SDSD Seronegative for Efficacy Analysis Set (63.0%; Table 7). The trend was reversed for dose intervals of ≥ 12 weeks, as participants who received LDSD typically had long dose intervals . There is a trend toward shorter dose intervals compared with DCO1. This is because the majority of the new participants included in the SDSD/LDSD Seronegative for Efficacy Analysis Set at DCO2 received SDSD, and had shorter dose intervals. Additionally this trend can be explained by the inclusion of COV005 (which had 3- to 5-week dose intervals), as well as by the inclusion of more participants enrolled in COV003, after the mandatory 2-dose regiment was implemented.

Table 7 Exposure to Study Intervention at the Time of Data cut-off

Parameter		SDSD + LDSD Seronegative for Efficacy Analysis Set		SDSD Seronegative for Efficacy Analysis Set		SDSD Seronegative for Efficacy Analysis Set (4-12 weeks dose interval)	
		AZD1222 (N = 8597)	**Control (N = 8581)**	**AZD1222 (N = 7201)**	**Control (N = 7179)**	**AZD1222 (N = 5849)**	**Control (N = 5763)**
Dose level [a], n (%)	LDSD	1396 (16.2)	1402 (16.3)	0	0	0	0
	SDSD	7201(83.8)	7179 (83.7)	7201 (100)	7179 (100)	5849 (100)	5763 (100)
Total		8597	8581	7201	7179	5849	5763
Dose interval, n(%)	< 6 weeks	3905 (45.4)	3871 (45.1)	3890 (54.0)	1698 (53.7)	3684 (63.0)	3653 (63.4)
	6-8 weeks	1124 (13.1)	1023 (11.9)	1112 (15.4)	1009 (14.1)	1112 (19.0)	1009 (17.5)
	9-11 weeks	1530 (17.8)	1594 (18.6)	906 (12.6)	958 (13.3)	906 (15.5)	958 (16.6)
	≥ 12 weeks	2038 (23.7)	2093 (24.4)	1293 (18.0)	1356 (18.9)	147 (2.5)	143 (2.5)
Total		8597	8581	7201	7179	5849	5763

[a] Dose level of control group is decided by the dose level of corresponding vaccine group.

Total row includes the number of participants with non-missing data for the corresponding characteristic and was used as the denominator for calculating percentages for all categories.

Source data: Main Safety Tables 1.2.1.2, 1.2.1.6, Supplemental Table IEMT182.3.2.1, Module 5.3.5.3

4.2.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics for the SDSD + LDSD Seronegative for Efficacy Analysis Set were well balanced (see Main Safety Tables 1.1.3.2 and 1.1.4.2) and were generally consistent with the Overall safety set (Any Dose for Safety Analysis Set, see Section 5.3). Overall, in the SDSD + LDSD Seronegative for Efficacy Analysis Set, approximately:

- 8% of participants were ≥ 65 years of age and mean age was approximately 42 years old
- 56% of participants were female
- 76% of participants were White, 10% were Black, 7% were other, 4% were Asian
- 36% of participants had a comorbidity at baseline

Demographics and baseline characteristics for the SDSD + LDSD Immunogenicity Analysis differed from the efficacy analysis set by design, as the immunology analysis set was enriched for older adults, for the AZD1222 group, and for diversity with regard to country (UK, Brazil, and South Africa). Overall, in the SDSD + LDSD Immunogenicity Analysis Set (see Immuno Tables 1.1.3.4 and 1.1.4.4), approximately:

- 12.1% of participants were ≥ 65 years of age and mean age was approximately 46 years old
- 55% of participants were female
- 78% of participants were White, 10% were Black, 6% were Other, 4% were Asian
- 36% of participants had a comorbidity at baseline

4.2.2 Efficacy Against COVID-19

4.2.2.1 Primary Endpoint: Efficacy Against COVID-19 Following Second Dose

The vaccine efficacy of AZD1222 was 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) in seronegative participants at baseline who received SDSD or LDSD and with follow up ≥ 15 days after the second dose (Table 8). This primary analysis of the primary endpoint met the statistical criterion of success as the lower bound of the CI was > 20%.

A sensitivity analysis of the primary endpoint using the ITT principle provided similar results to those observed for the primary analysis (Table 8).

In the population of patients who received SDSD, vaccine efficacy was 63.09% (95% CI: 51.81%, 71.73%) (Table 8). In an analysis of participants who received SDSD with a dose interval of 4-12 weeks, vaccine efficacy was 58.80 (95% CI: 44.63%, 69.64%).

From the time of DCO1 to DCO2, there was a large increase in the number of participants evaluable and the number of COVID-19 cases in all 4 analysis sets, as shown in Table 8. The data reported on DCO2 are consistent across different analysis sets, and are also consistent with data reported for DCO1.

Table 8 Primary Endpoint - Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose

Analysis population	Participants with events				VE (%)	95% CI (%)	P-value
	AZD1222		Control				
	N	n (%)	N	n (%)			
Primary endpoint: SDSD + LDSD, seronegative [a]	8597	84 (0.98)	8581	248 (2.89)	66.73	(57.41, 74.01)	<0.001
SDSD + LDSD ITT, seronegative [a]	8603	86 (1.00)	8586	246 (2.87)	65.65	(56.11, 73.11)	<0.001
SDSD, seronegative[a]	7201	74 (1.03)	7179	197 (2.74)	63.09	(51.81, 71.73)	<0.001
SDSD, seronegative, 4-12 weeks dosing interval [b]	5849	65 (1.11)	5763	156 (2.71)	58.80	(44.63, 69.64)	<0.001

[a] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the terms of study code, treatment, age group at screening (18-55, 56-69, and ≥70 years) as covariates, as well as the log of the follow-up time as an offset.

VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

The efficacy objective is met if the lower bound of the CI for the VE must be > 20%. P-value testing null hypothesis that VE is equal to 20% is presented.

[b] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 95% CI (or 97.5% one-sided) and p value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55 years, 56-69 years, and >=70 years) as strata factors as well as the log of total number of participants for each combination of treatment and strata.

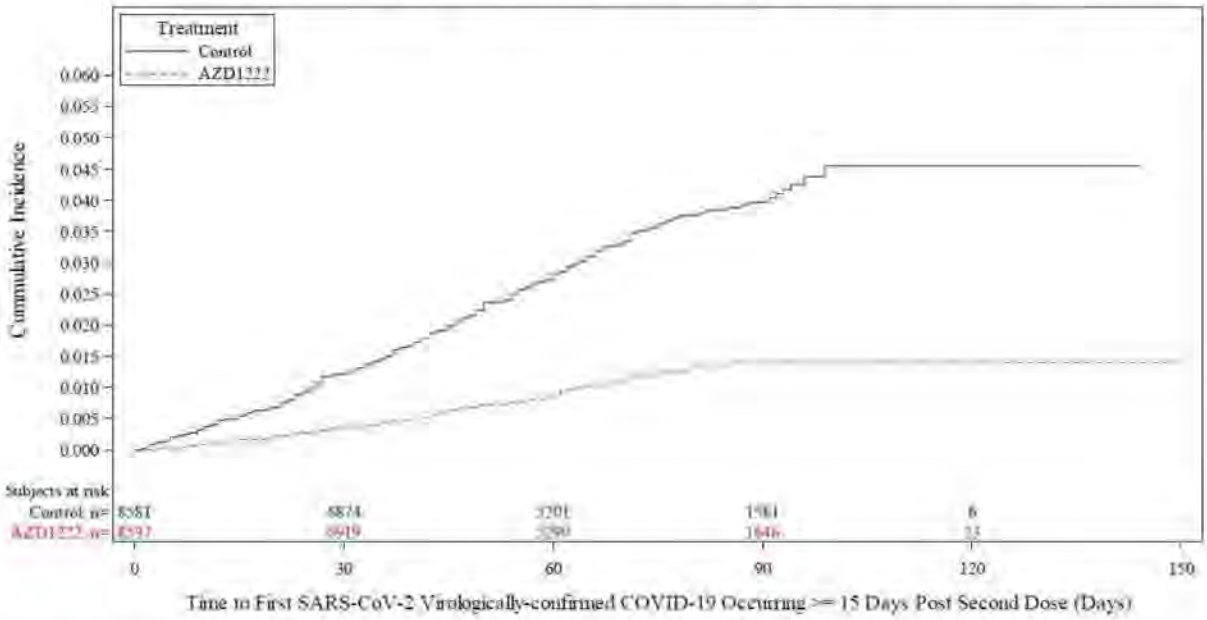
VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 95% (or 97.5% one-sided) CI for the VE is obtained by taking 1 minus the 95% (or 97.5% one-sided) CI of the risk ratio derived from the model. If the maximum likelihood estimate of VE is 100% or negative infinity, the exact 97.5% one-sided CI is reported.

The observation period for the endpoint was 15 days post second dose up to 1 year in study.

COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test. COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade ≥ 4.
Source: Main Efficacy Tables 1.3.1.1, 1.3.1.2, 1.3.1.3. and Supplemental Table IEMT141.1.1.2, Module 5.3.5.3.

A Cumulative Incidence curve of the time to first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention is presented in Figure 3, showing clear early separation of the curve for the AZD1222 group from the control group that continues to diverge over time.

Figure 3 **Cumulative Incidence Plot for Time to First SARS CoV 2 Virologically Confirmed Symptomatic COVID 19 Occurring ≥ 15 Days Post Second Dose (SDSD + LDSD Seronegative for Efficacy Analysis Set)**

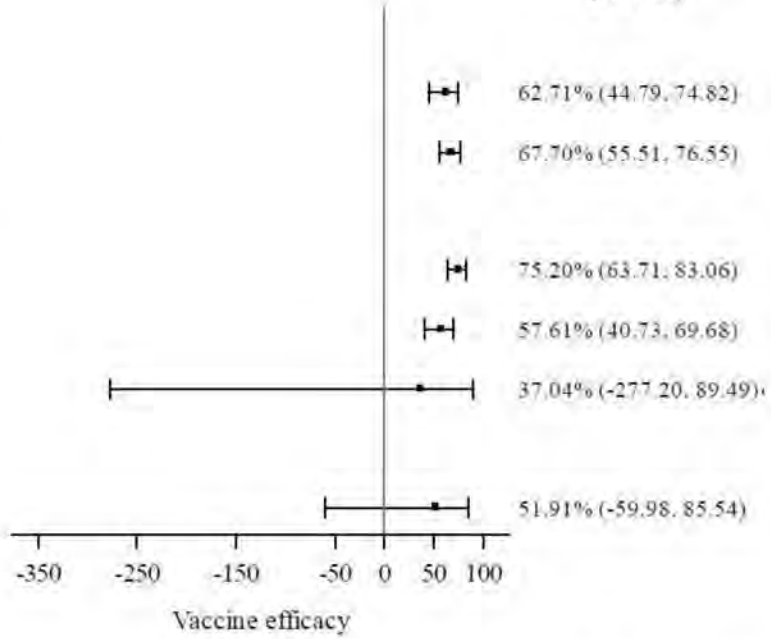


The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring ≥ 15 days post second dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of second dose of study intervention + 15) +1. For censored participants, the censoring time is from date of second dose of study intervention + 15 to last observed time during the analysis period.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 endpoints are based on adjudicated events.
Source: Main Efficacy Figure 1.3.2.1, Module 5.3.5.3.

Subgroup analyses of the primary endpoint showed efficacy of the AZD1222 vaccine against COVID-19 for the subgroup categories of comorbidity, age, and country (the UK and Brazil) that was consistent with the primary endpoint (Figure 4). The assessment of vaccine efficacy in older adults was underpowered for determination of effect. Results from each of these subgroup is discussed in more detail in Sections 4.2.5, 4.2.6, and 4.2.7, respectively.

Figure 4 **Subgroup Analysis of Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose - Forest Plot (SDSD + LDSD Seronegative for Efficacy Analysis Set)**

	AZD1222 (N=8597)		Control (N=8581)		
Subgroup	Number of Participants	Observed Events	Number of Participants	Observed Events	Vaccine efficacy (95% CI)
Comorbidity at Baseline					
Yes	3056	34 (1.11)	3102	93 (3.00)	62.71% (44.79, 74.82)
No	5241	50 (0.95)	5156	149 (2.89)	67.70% (55.51, 76.55)
Country					
United Kingdom	4427	33 (0.75)	4521	133 (2.94)	75.20% (63.71, 83.06)
Brazil	3414	49 (1.44)	3339	112 (3.35)	57.61% (40.73, 69.68)
South Africa	756	2 (0.26)	721	3 (0.42)	37.04% (-277.20, 89.49)
Age group at screening					
65 years and above	703	4 (0.57)	680	8 (1.18)	51.91% (-59.98, 85.54)



VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset.
VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was from 15 days post second dose up to 1 year in study.
COVID-19 endpoints were based on adjudicated events.
Source: Supplemental Figure IEMT 241, Module 5.3.5.3.

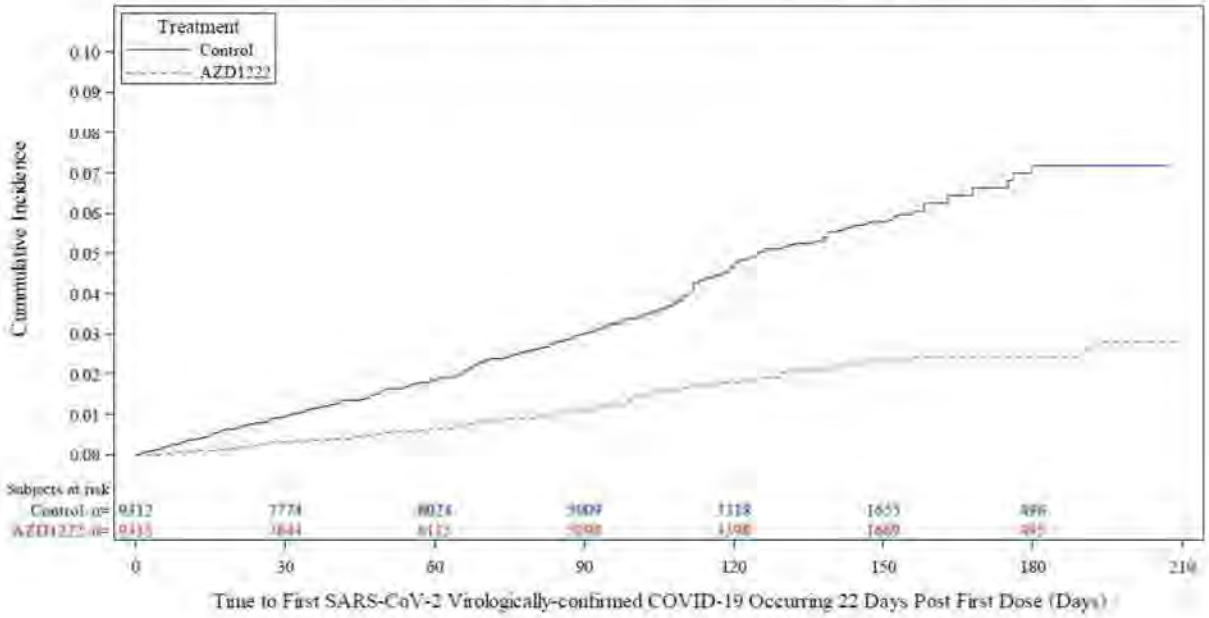
4.2.2.2 Efficacy Against COVID-19 Following First Dose

Efficacy of AZD1222 against COVID-19 was observed in participants seronegative at baseline who received a SD as the first dose with follow up ≥ 22 days post first dose. The vaccine efficacy was 61.55% (95% CI: 52.91%, 68.61%) (see Main Efficacy Table 1.4.10.1). This included participants who later received a second dose or were scheduled to receive a second dose, and those who received only a single dose (see Figure 2).

A further analysis was performed to evaluate efficacy against COVID-19 following only a single dose. The follow-up time for this analysis began at 22 days after the first dose and with censoring at the earliest time point of when the participant received a second dose or at 12 weeks post the first dose. In this analysis, vaccine efficacy was 71.42% (95% CI: 51.11%, 84.08%) for participants who received SD as first dose, and 69.23% (95% CI: 48.54%, 82.35%) for participants who received any dose and 22 days after the first dose (see Supplemental Table IEMT98.1.1, Module 5.3.5.3).

A Cumulative Incidence curve of the time to first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥ 22 days post first dose shows divergence of the curve for the AZD1222 group (Dose 1 SD seronegative group) from the control group following the first dose (Figure 5). These data support persistence of efficacy up to 6 months into the follow-up period, after which there is data scarcity.

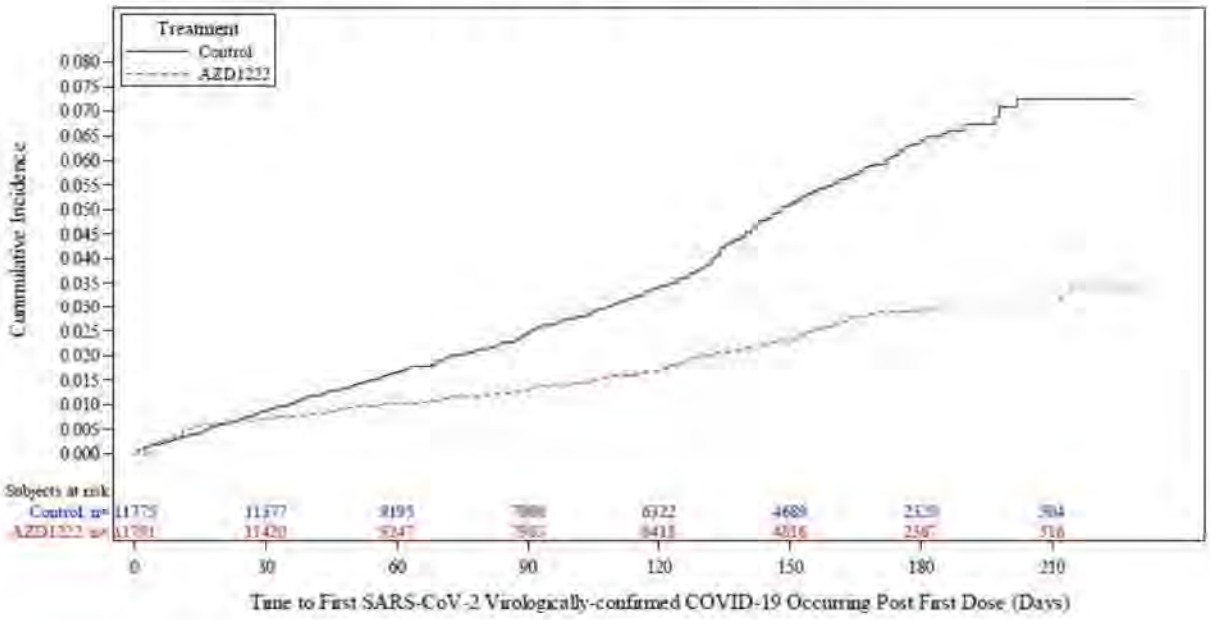
Figure 5 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed COVID -19 Occurring 22 Days Post First Dose of Study Intervention (Dose 1 SD Seronegative for Efficacy Analysis Set)



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring >= 22 days post first dose of study intervention, in days, has been calculated as follows:
Date of SARS-CoV-2 virologically confirmed test - (date of first dose of study intervention + 22) + 1. For censored participants, the censoring time is from date of first dose of study intervention + 22 to last observed time during the analysis period.
The observation period for the endpoint was 22 days post first dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically confirmed results from RT-PCR or other nucleic acid amplification test.
Source: Main Efficacy Figure 1.4.11.1., Module 5.3.5.3

An analysis was also conducted in the full efficacy population (ie, Any dose for Efficacy Analysis set, any serostatus), who received at least one dose with follow up from the first dose. Efficacy of the AZD1222 vaccine against COVID-19 was 50.53% (95% CI: 42.28%, 57.61%) in this group of participants (see Main Efficacy Table 1.4.8.1, , Supplemental Table IEMT◦98.1.1). Examination of the Cumulative Incidence curves in Figure 6 shows that the curves begin to diverge approximately 21 days after the first dose, indicating induction of protective immunity by 21 days with the first dose.

Figure 6 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus)



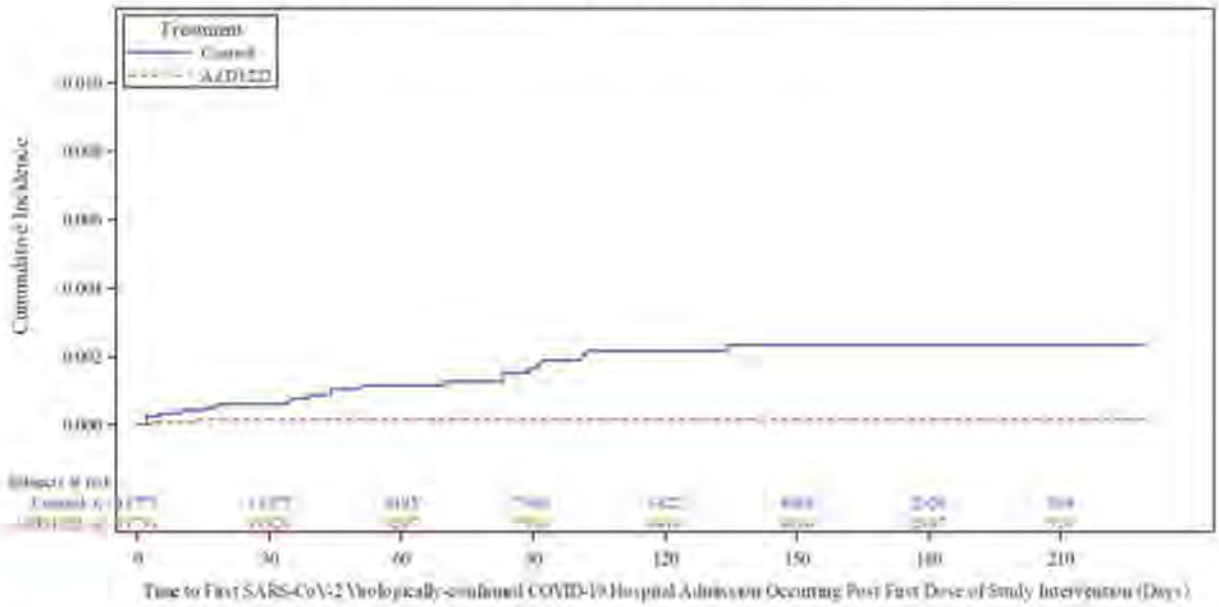
The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of first dose of study intervention +1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.
The observation period for the endpoint was post first dose up to 1 year in study.
COVID endpoints are based on adjudicated events.
Source: Main Efficacy Figure 1.4.9.1, Module 5.3.5.3.

4.2.3 Efficacy Against COVID-19 Hospital Admission and Severe COVID-19 Disease

AZD1222 provided complete protection against COVID-19 hospital admission. At DCO2, there were 9 cases of COVID-19 hospital admission in the Control group and no cases in the AZD1222 group (Table 9) in the SDSD + LDSD seronegative population. Data for the SDSD Seronegative for Efficacy Analysis Set (any interval and 4-12 weeks dosing interval) are also shown in Table 9, and are consistent with the primary population.

When analysis was done in the full efficacy population (Any Dose for Efficacy Analysis Set) with follow-up post first dose, there were 22 cases of COVID-19 hospital admissions and 3 severe COVID-19 cases, one of which was fatal (Table 9) among the 11776 Control group recipients. In contrast, among the 11794 AZD1222-treated participants, there were only 2 cases of COVID-19 hospital admissions and no cases of severe COVID-19 (see Main Efficacy Tables 1.4.2.1, 1.4.14.1, and 1.4.17.1, Module 5.3.5.3). The Cumulative Incidence curve in the Any Dose for Efficacy Analysis Set with follow-up post first dose shows that the two cases of COVID-19 hospitalisation in the vaccine recipients occurred on Days 1 and 10 post vaccination. After the vaccine-induced immune response had matured, no subsequent COVID-19 hospitalisations accumulated (Figure 7).

Figure 7 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Hospital Admission Occurring Post First Dose (Any Dose for Efficacy Analysis Set)



The time to first SARS-CoV-2 virologically-confirmed hospital admission occurring post first dose of study intervention, in days, has been calculated as follows:
Date of SARS-CoV-2 virologically-confirmed test – (date of first dose of study intervention) +1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.

The observation period for the endpoint was from first dose up to 1 year in study. COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
COVID-19 hospital admission is defined as WHO clinical progression scale ≥ 4.
Source: Supplemental Figure IEMT 227, Module 5.3.5.3

Table 9 Vaccine Efficacy Against COVID-19 Hospital Admissions

Analysis population	Time period of endpoint	Participants with events, n (%)				VE (%)	97.5% [a] CI (%)	p-value
		N	AZD1222	N	Control			
SDSD + LDSD, seronegative	≥ 15 days post second dose	8597	0	8581	9 (0.10)	100 [a]	(50.19, NE) [a]	0.004 [a]
SDSD, seronegative	≥ 15 days post second dose	7201	0	7179	8 (0.11)	100	(42.58, NE) [a]	0.007
Dose 1 SD, seronegative	≥ 22 days post first dose	9335	0	9312	14 (0.15)	100 [a]	(69.92, NE) [a]	<0.001
SDSD 4-12 weeks dose interval	≥ 15 days post second dose	5849	0	5763	8 (0.14)	100	(42.65, NE) [a]	0.007
Any dose	Post first dose	11794	2 (0.02) [c]	11776	22 (0.19)	90.92	(63.06, 98.97)	<0.001

[a] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55, 56-69, and ≥70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1-(incidence of the infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

[b] These two cases occurred on Days 1 and 10 post vaccination.

COVID-19 endpoints were based on adjudicated events. COVID-19 Hospitalisation defined as WHO severity grading ≥ 4 based on WHO clinical progression scale (Table 5).

Source: Main Efficacy Tables 1.4.13.1, 1.4.13.2, 1.4.14.1, 1.4.15.1, and Supplemental Table IEMT 141.1.5.2.

The trend for protection against severe COVID-19, referring to all case definitions with a WHO severity grading ≥ 6, in participants who received AZD1222, was also observed at DCO2, although the number of cases was too low to inferentially assess vaccine efficacy (Table 10).

Table 10 Vaccine Efficacy Against COVID-19 Severe Disease

Analysis population	Time period of endpoint	Participants with events, n (%)				VE (%)	97.5%[a] or 95%[b] CI (%)	p-value
		N	AZD1222	N	Control			
SDSD + LDSD, seronegative	≥ 15 days post second dose	8597	0	8581	2 (0.02)	100[a]	(-432.68, NE)[a]	0.500
SDSD, seronegative	≥ 15 days post second dose	7201	0	7179	1 (0.01)	100	(-3742.53, NE)[a]	0.993
Dose 1 SD, seronegative	≥ 22 days post first dose	9335	0	9312	2 (0.02)	100[a]	(-437.45, NE)[b]	>0.505[b]
SDSD 4-12 weeks dose interval	≥ 15 days post second dose	5849	0	5763	1 (0.02)	100	(-3747.32, NE)	0.993
Any dose	Post first dose	11794	0	11776	3 (0.03)	100	(-143.63, NE)	0.253

[a] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55, 56-69, and ≥70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

[b] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

COVID-19 endpoints were based on adjudicated events.

Source: Main Efficacy Tables 1.4.1.1, 1.4.1.2, 1.4.2.1, 1.4.3.1 and Supplemental Table IEMT141.1.2.2.

4.2.4 Efficacy Against SARS-CoV-2 Infection

Study COV002 included active monitoring of infection through weekly self-swabbing. Code-bar tagged swabs were distributed to participants to support weekly traceable results of self-swabbing for detection of SARS-CoV-2 infection. Swabs were sent for RT-PCR testing at National Health Service (NHS) laboratories. Participants were also asked to self-record whether they experienced symptoms or not. Participants who had a virologically confirmed SARS-CoV-2 infection and reported that they had no symptoms are referred to here as 'asymptomatic'; those participants who did not report whether they had symptoms or not are referred to here as 'unknown'.

In analysis of efficacy against any virologically confirmed COVID-19 infection, which includes cases that were symptomatic, asymptomatic, symptomatic non-primary, and unknown, vaccine efficacy in the primary population was 53.71% (95% CI 41.36%, 63.47%) (Table 11). No efficacy of AZD1222 was observed against asymptomatic SARS-CoV-2 infection in either the LDSD or SDSD groups (see Main Efficacy Tables 1.4.4.1, 1.4.4.2, 1.4.4.3, Module 5.3.5.3) (Table 11).

Table 11 Vaccine Efficacy for Incidence of Asymptomatic SARS-CoV-2 Infection Occurring ≥ 15 Days Post Second Dose (for Study COV002 only)

Analysis population	COVID-19 case definition	Participants with events, n (%)				VE (%)	95% CI (%)	Nominal P-value
		N	AZD1222	N	Control			
SDSD + LDSD for COV002, seronegative	Asymptomatic SARS-CoV-2 infection [a]	4071	27 (0.66)	4136	33 (0.80)	18.55	(-35.40, 51.01)	0.429
	Any virologically confirmed infection [b]	4071	100 (2.46)	4136	215 (5.20)	53.71	(41.36, 63.47)	-
SDSD for COV002, seronegative	Asymptomatic SARS-CoV-2 infection [a]	2692	20 (0.74)	2751	19 (0.69)	-5.64	(-97.86, 43.60)	0.864
	Any virologically confirmed infection [b]	2692	71 (2.64)	2751	127 (4.62)	43.90	(25.04, 58.01)	-

[a] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of study code, treatment, age group at screening (18-55 years, 56-69 years, and ≥ 70 years) as covariates as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

[b] Based on all symptomatic, asymptomatic, symptomatic non-primary, and unknown symptoms cases. VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression. The 95% (or 97.5% one-sided) CI for the VE is obtained by taking 1 minus the 95% (or 97.5% one-sided) CI of the risk ratio derived from the model. If the maximum likelihood estimate of VE is 100% or negative infinity, the exact 97.5% one-sided CI is reported. VE of AZD1222 versus control and the 95% CI were estimated based on Poisson regression with robust variance including treatment as covariate as well as the log of the follow-up time as an offset.

COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.

Source: Main Efficacy Tables 1.4.4.1, 1.4.4.2, Supplemental Table IEMT 218.1, 218.2, Module 5.3.5.3

4.2.5 Efficacy Against COVID-19 in Adults with Comorbid Conditions at Baseline

The AZD1222 vaccine provided protection against COVID-19 in adults with comorbid conditions at baseline, which was consistent with the level of protection in the general study population. Vaccine efficacy estimates ≥ 15 days post second are shown in Table 12.

Table 12 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 15 Days Post Second Dose in Adults with a Comorbid Condition at Baseline

Analysis Set Comorbidity at baseline	Participants with events, n (%)		VE (%)	95% CI	Nominal p-value
	AZD1222 n / N (%)	Control n / N (%)			
SDSD + LDSD Seronegative for Efficacy					
Yes	34 / 3056 (1.11)	93 / 3102 (3.00)	62.71	(44.79, 74.82)	<0.001
No	50 / 5241 (0.95)	149 / 5156 (2.89)	67.70	(55.51, 76.55)	<0.001
SDSD Seronegative for Efficacy					
Yes	28 / 2592 (1.08)	76 / 2631 (2.89)	62.20	(41.71, 75.49)	<0.001
No	46 / 4309 (1.07)	115 / 4227 (2.72)	61.62	(45.98, 72.73)	<0.001
SDSD Seronegative for Efficacy (4-12 weeks dose interval)					
Yes	25 / 2197 (1.14)	60 / 2173 (2.76)	58.40	(33.69, 73.90)	<0.001
No	40 / 3624 (1.10)	94 / 3564 (2.64)	59.23	(40.99, 71.83)	<0.001

VE of AZD1222 versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.
VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test. COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade >= 4.
Source: Supplemental Table IEMT 219.2.a, 219.2.b, 175.1.a, 175.1.b, 175.2.a, 175.2.b, Module 5.3.5.3.

4.2.6 Efficacy Against COVID-19 in Older Adults (≥ 65 years of age)

At the time of DCO2, 1383 total participants age 65 or greater were enrolled and included in the primary efficacy population (SDSD + LDSD Seronegative for Efficacy Analysis Set) (N = 703 for AZD1222 and N = 680 for control) (see Age Safety Table 4.1.3.2.b, Module 5.3.5.3). All participants aged ≥ 65 years received SDSD, with a majority having a dose interval of < 6 weeks (89.6% for AZD1222 group, and 87.8% for the control group; see Age Safety Table 4.2.1.6.b, Module 5.3.5.3); therefore, for the subgroup of ≥ 65 years the SDSD Seronegative for Efficacy Analysis Set is identical to the SDSD + LDSD Seronegative for Efficacy Analysis Set.

The median duration of follow-up after the first dose was 78.0 days and 33.0 days 15 (or greater) days after the second dose, the latter representing an increase from the 20.0 days reported for DCO1 (see Age Efficacy Table 4.4.12.1, Module 5.3.5.3). A large proportion (87.8%) of older adults received their second dose <6 weeks after their first (see Age Safety Table 4.2.1.1b, Module 5.3.5.3).

In the SDSD Seronegative for Efficacy Analysis Set, 4 participants in the AZD1222 group and 8 participants in the Control group had a case of COVID-19 ≥ 15 days after the second dose; data were similar for participants with a 4-12 weeks dose interval (Table 13). A cumulative incidence plot for the SDSD Seronegative for Efficacy Analysis Set is shown in Figure 8. Note that a single event produces a much greater step in the cumulative incidence curve the later in follow-up that the event occurs, due to the reduced number of participants at risk at that time. AZD1222 has fewer number of events overall (4) vs control (8), but the last event in AZD1222 occurs later in follow-up, which leads to a larger step in the curve.

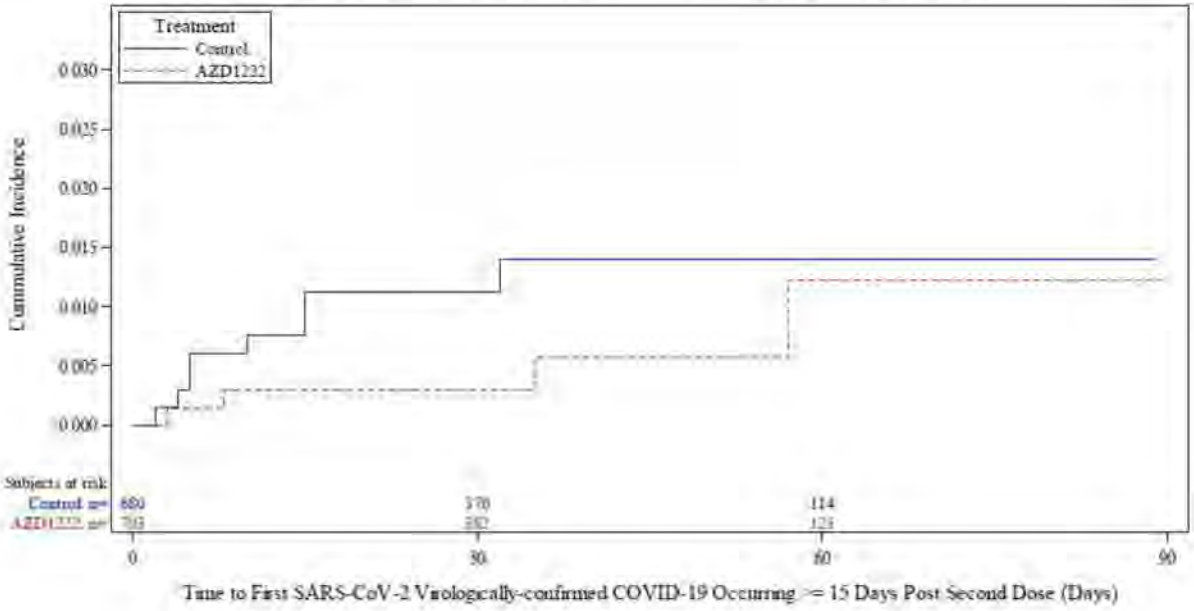
Table 13 **Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose in the Age Subgroup ≥ 65 Years (SDSD Seronegative for Efficacy Analysis Set, SDSD Seronegative for Efficacy Analysis Set, Dose Interval 4-12 Weeks)**

Analysis set Age subgroup	Participants with events		VE (%)	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
SDSD seronegative for efficacy analysis set, any dosing interval[a]					
≥ 65 years	4 / 703 (0.57)	8 / 680 (1.18)	51.91	(-59.98, 85.54)	0.233
SDSD seronegative for efficacy analysis set, 4–12 weeks dosing interval					
≥ 65 years	4 / 687 (0.58)	7 / 666 (1.05)	44.82	(-88.81, 83.88)	0.343

[a] As all participants aged ≥ 65 years received SDSD, data are identical for the SDSD + LDSD Seronegative for Efficacy Analysis Set.

VE of AZD1222 versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.
VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically confirmed results from RT-PCR or other nucleic acid amplification test.
COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade ≥ 4.
The 4 to 12 weeks dosing interval range corresponds to ≥ 28 days to ≤ 84 days.
Source: Tables 4.3.1.1 and 4.3.1.2; Supplemental Table IEMT 141.4.1.2.

Figure 8 **Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days After Second Dose in Adults ≥ 65 Years (SDSD Seronegative for Efficacy Analysis Set)**



The time to first SARS-CoV-2 virologically-confirmed COVID-19 occurring >= 15 days post second dose of study intervention, in days, has been calculated as follows:
Date of SARS-CoV-2 virologically-confirmed test – (date of second dose of study intervention + 15) +1. For censored participants, the censoring time is from date of second dose of study intervention + 15 to last observed time during the analysis period.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade >= 4.
Source: Age Figure 4.3.2.2, Module 5.3.5.3.

In the Dose 1 SD Seronegative for Efficacy Analysis Set ≥ 22 days after the first dose, there were 6 cases in the AZD1222 group and 13 in the Control group (Table 14). In the AZD1222 vaccine group, no COVID-19 hospital admissions or severe COVID-19 cases were reported in older adults, whereas in the Control group, 2 of the 13 cases required hospitalisation. A similar trend was observed in the full efficacy population, where none of the 10 cases in the AZD1222 group and 4 of the 20 cases in the Control group required hospital admission (Table 15). A cumulative incidence plot for the full efficacy population is shown in Figure 9.

Table 14 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 22 Days Post First Dose in Adults ≥ 65 years of Age (Dose 1 SD Seronegative for Efficacy Analysis Set)

COVID-19 case definition	Participants with events, n (%)		VE (%)	95% [a] or 97.5% [b] CI	Nominal p-value
	AZD1222 (N = 945)	Control (N= 896)			
COVID-19 (primary case definition)	6 (0.63)	13 (1.45)	55.87 [a]	(-16.08, 83.22) [a]	0.097 [a]
COVID-19 hospitalisation	0	2 (0.22)	100 [b]	(-404.85, NE) [b]	0.474 [b]
COVID-19 severe disease	0	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 death	0	[redacted]	[redacted]	[redacted]	[redacted]

[a] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

[b] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55, 56-69, and ≥70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

The observation period for the endpoint was from the first dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events.

Source: Age Efficacy Tables 4.4.10.1, 4.4.3.1, 4.4.15.1, and 4.4.18.1, Supplemental Table IEMT 212.2.2, Module 5.3.5.3

Table 15 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring Any Time Post First Dose in Adults ≥ 65 years of Age (Any Dose for Efficacy Analysis Set)

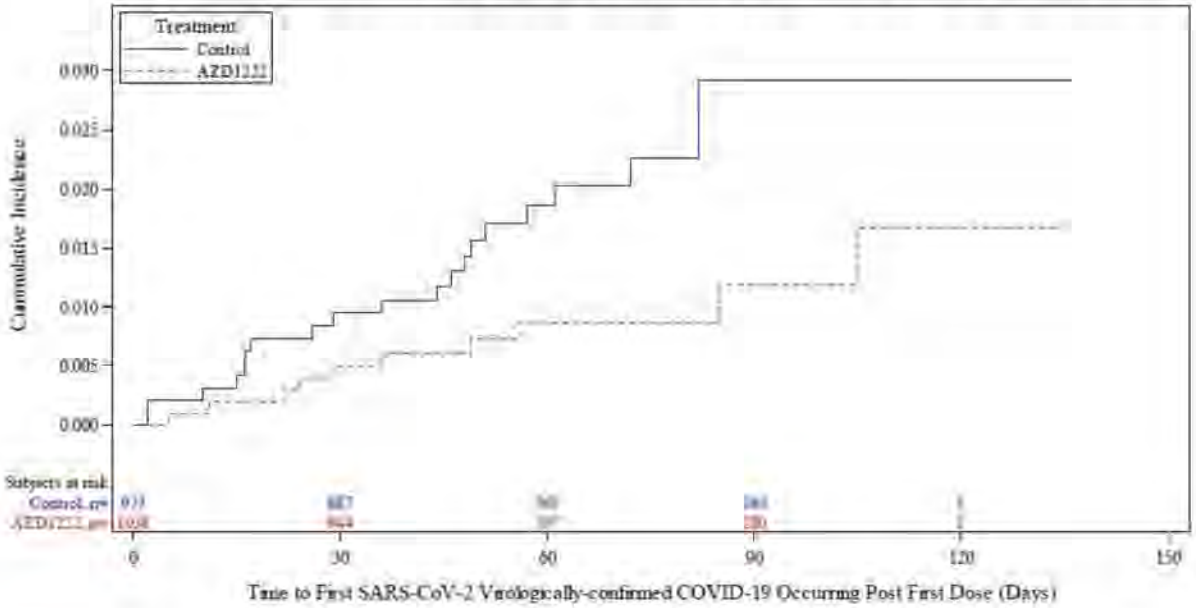
COVID-19 case definition	Participants with events, n (%)		VE (%)	95% [a] or 97.5% [b] CI	Nominal p-value
	AZD1222 (N = 1038)	Control (N= 973)			
COVID-19 (primary case definition)	10 (0.96)	20 (2.06)	52.99 [a]	(-0.46, 78.00) [a]	0.051 [a]
COVID-19 hospitalisation	0	4 (0.41)	100 [b]	(-42.00, NE) [b]	0.110 [b]
COVID-19 severe disease	0	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 death	0	[redacted]	[redacted]	[redacted]	[redacted]

[a] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

[b] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55, 56-69, and ≥70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

Source: Age Efficacy Tables 4.4.2.1, 4.4.8.1, 4.4.14.1, 4.4.17.1, Module 5.3.5.3.

Figure 9 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring Post First Dose of Study Intervention in Adults ≥ 65 Years of Age (Any Dose for Efficacy Analysis Set)



The time to first SARS-CoV-2 virologically-confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows:
Date of SARS-CoV-2 virologically-confirmed test - date of first dose of study intervention + 1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.
The observation period for the endpoint was from first dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade >= 4.
Source: Age Figure 4.4.9.1, Module 5.3.5.3.

Taken together, these data suggest that the AZD1222 vaccine provides protection against COVID-19 in older adults that is consistent with the general study population. Moreover, these data further support earlier findings in the older adults group reported at DCO1.

4.2.7 Efficacy by Country

At DCO2, COV001 (UK) and COV005 (South Africa) are included in the pooled analysis, as there have been ≥ 5 cases in the primary efficacy population ≥ 15 days after the second dose.

Consequently, for DCO2, efficacy data is presented for South Africa, and in the UK subgroup is presented for both COV001 and COV002 studies.

For the primary efficacy analysis population (SDSD + LDSD, seronegative), the baseline characteristics were broadly comparable for participants in the UK, Brazil, and South Africa. Of note, there were fewer participants with comorbidities at baseline in South Africa (22.7%) than in the UK (35.9%) or Brazil (38.7%) (see Country Safety Tables 3.1.4.2.a, 3.1.4.2.b, 3.1.4.2.c, Module 5.3.5.3). Additionally, participants in South Africa were younger than those in Brazil and the UK, and the majority of participants in South Africa were Black, whilst the majority in Brazil and UK were White (see Country Efficacy Tables 3.1.3.2.a, 3.1.3.2.b and 3.1.3.2.c, Module 5.3.5.3).

The dose interval and dose levels for the primary efficacy analysis population were also different between the 3 countries (see Country Efficacy Tables 3.2.1.2.a, 3.2.1.2.b, 3.2.1.2.c, Module 5.3.5.3). Participants in the UK had a range of dose intervals, and 43.4% had a dose interval ≥ 12 weeks. The majority of participants in Brazil and South Africa had dose intervals of < 6 weeks (Brazil 72.3%, South Africa 93.7%), and no participants in South Africa had a dose interval of ≥ 12 weeks. In the UK, approximately two-thirds of participants (68.9%) received SDSD and one-third (31.1%) received LDSD. In South Africa, a small number of participants received LDSD (2.2%). In Brazil, all participants received SDSD. Dose interval data were similar for the SDSD Seronegative for Efficacy Analysis Sets, with slightly fewer participants in the UK having a dose interval of ≥ 12 weeks (38.6%) (see Country Safety Tables 3.2.1.6.a, 3.2.1.6.b, and 3.2.1.6.c, Module 5.3.5.3).

The median duration of follow-up time from 15 days post second dose in the AZD1222 groups was longer for the UK (81.0 days) and South Africa (80.0 days) than for Brazil (54.0 days) (see Country Efficacy Table 3.4.12.1, Module 5.3.5.3).

In the UK and Brazil, the AZD1222 vaccine provided protection against COVID-19 in seronegative participants at baseline who received SDSD or LDSD with follow-up ≥ 15 days post second dose (Table 16 and see Table 25 of the Summary of Clinical Efficacy for SDSD analysis only). In the primary efficacy population, vaccine efficacy trended higher in the UK than Brazil. This difference is likely due to the longer dose intervals in the UK, since in the SDSD Seronegative Efficacy Analysis Set (with 4-12 weeks dosing interval), vaccine efficacy was similar in the UK and Brazil (see Table 26 of the Summary of Clinical Efficacy).

In South Africa, there were a total of 5 cases ≥ 15 days after the second dose, 2 in the AZD1222 group and 3 in the Control group (Table 16).

Table 16 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 15 Days Post Second Dose in Adults by Country (SDSD + LDSD Seronegative for Efficacy Analysis Set)

COVID-19 case definition	Participants with events, n (%)		VE (%)	95%[a] or 97.5%[b] CI	Nominal p-value
	AZD1222	Control			
UK	**N = 4427**	**N= 4521**			
COVID-19 (primary case definition)	33 (0.75)	133 (2.94)	75.20[a]	(63.71, 83.06)[a]	<0.001[a]
COVID-19 hospitalisation	0	[redacted]	[redacted][b]	[redacted][b]	[redacted][b]
COVID-19 severe disease	0	[redacted]	[redacted][b]	[redacted][b]	[redacted][b]
COVID-19 death	0	[redacted]	[redacted]	[redacted]	[redacted]
BRAZIL	**N = 3414**	**N = 3339**			
COVID-19 (primary case definition)	49 (1.44)	112 (3.35)	57.61[a]	(40.73, 69.68)[a]	<0.001[a]
COVID-19 hospitalisation	0	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 severe disease	0	[redacted]	[redacted][b]	[redacted][b]	[redacted]
COVID-19 death	0	0	-	-	-
SOUTH AFRICA	**N = 756**	**N = 721**			
COVID-19 (primary case definition)	2 (0.26)	3 (0.43)	37.04	(-277.20, 89.49)	0.612[a]
COVID-19 hospitalisation	0	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 severe disease	0	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 death	0	[redacted]	[redacted]	[redacted]	[redacted]

[a] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

[b] The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code and age group at screening (18-55, 56-69, and ≥70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

The observation period for the endpoint was from 15 days post second dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events.

Source: Country Efficacy Tables 3.3.1.1.a, 3.4.1.1.a, 3.4.13.1.a, 3.4.16.1.a, 3.4.19.1.a, 3.3.1.1.b, 3.4.1.1.b, 3.4.13.1.b, 3.4.16.1.b, and 3.4.19.1.b, 3.3.1.1.a, 3.4.1.1.c, 3.4.13.1.c, 3.4.16.1.c, Module 5.3.5.3

AZD1222 conferred protection after the first dose in the UK and Brazil, with vaccine efficacy of over 50% in the UK and Brazil (Any Dose for Efficacy Analysis Set post first dose; see Table 27 of the Summary of Clinical Efficacy). With a follow-up time starting at 22 days post first dose, vaccine efficacy was approximately 60% in the UK and Brazil (see Table 27 of the Summary of Clinical Efficacy). As described above (Section 4.2.2), AZD1222 provides protection from approximately 21 days after first dose.

Vaccine efficacy data for South Africa are presented in Table 30 of the Summary of Clinical Efficacy. Due to the low number of cases in each analysis set, it is not possible to reach a conclusion on the efficacy of AZD1222 in South Africa; however, no cases of severe COVID-19 or COVID-19 hospitalisation were reported in South Africa.

4.2.8 Humoral Immunogenicity

Humoral immunogenicity was analysed using a validated multiplexed immunoassay in which the quantitative responses to Spike and RBD are measured, and a validated pseudoneutralisation assay using a lentiviral vector platform at an IC_{50}, and with a qualified live neutralisation assay using SARS-CoV-2 strain derived from SARS-CoV-2 Victoria/1/2020 analysed at the Neutralisation Dilution 50 measurement.

As previously stated, the immunogenicity analysis set was enriched for participants ≥ 65 years of age, for a larger proportion of participants receiving AZD1222 participants than control. Additionally, a more diverse regional and racial makeup as compared with the efficacy analysis set was included to provide larger group sizes in order to better interpret immunogenicity in these subpopulations. Approximately 15% of the overall safety analysis set was targeted for inclusion in the immunogenicity analysis set, with more samples analysed on the Spike/RBD binding assays as compared to the cell-based pseudoneutralisation assay (targeted for up to 8% of subjects in safety analysis set) due to logistic constraints. Live neutralisation assays were performed to complement the nAb results from the pseudoneutralisation assay.

RBD-binding antibody response was closely correlated with S-binding antibody response for all analyses; therefore, only the S-binding antibody response is presented and discussed in the summary. For the RBD-binding antibody levels and seroconversion rates 28 days after the first dose and 28 days after the second dose see Tables 31 and 33, respectively, of the Summary of Clinical Efficacy). All data discussed in this section are for seronegative participants at baseline, unless otherwise stated.

As of 07 December 2020, the full immunogenicity population (ie, SDSD + LDSD for Immunogenicity Analysis Set) included 3712 participants (15.3% of the Any Dose for Safety Analysis Set), 2135 of whom had received AZD1222 and 1577 of whom had received a

control. For participant disposition of the Immunogenicity Analysis Sets, see Immuno Table 1.1.1.2, Module 5.3.5.3.

The results presented in this section demonstrate that, as shown previously at DCO1, AZD1222 promotes a strong induction of humoral immunogenicity, as measured by anti-S, anti-RBD, and nAb to SARS-CoV-2. This effect was observed in the combined (SDSD + LDSD) immunogenicity analysis set, as well as in the separate SDSD and LDSD analysis sets.

4.2.8.1 Rate of Seroconversion

The rate of seroconversion (≥ 4-fold increase from baseline) by S-binding antibodies at DCO2 was ≥ 98.5% at 28 days after the first dose and > 99.5% at 28 days after the second dose for seronegative participants at baseline in the pooled combined (SDSD + LDSD) immunogenicity analysis set, as well as in both the SDSD and LDSD analysis sets. A similar trend was observed for nAb. The rate of seroconversion with a live neutralisation assay was high (> 80%) at 28 days after the first dose and > 99% at 28 days after the second dose analysis set, consistent with data from DCO1 (see Table 31 at the Summary of Clinical Efficacy, and Immuno Tables 1.7.2.3.1, 1.7.2.3.2, and 1.7.2.3.3, Module 5.3.5.3). These results are consistent with data published for Study COV001 (Folegatti et al, 2020a, and Barrett et al 2020).

4.2.8.2 Quantification of Anti-S and nAb Titres

At DCO2, an increase in S-binding antibodies was observed at 28 days after the first dose (GMT = 8104.51) for seronegative participants at baseline in the combined (SDSD + LDSD) immunogenicity analysis set, with a notable further increase at 28 days following the second dose (GMT = 31496.64) (see Immuno Table 1.7.1.1.1, Module 5.3.5.3). These results were consistent with data reported at DCO1.

Of note, baseline seropositive participants also had increased S-binding responses after a first dose, with a GMT = 140020.35 (95% CI: 98697.5, 198644.4) over baseline values (GMT = 10741.99 [95 % CI: 6579.4, 17538.3]). In contrast to the baseline seronegative group, antibody levels were not further increased by a second dose, which is consistent with an 'immune plateau' noted with other vaccines. The ability to induce an immune response in persons who already have high titres of antibodies to SARS-CoV-2 is a notable finding, given the increasing incidence of infection and serosurveys suggesting that in some high-risk populations, such as healthcare workers and urban residents, over 16% of the population are seropositive to SARS-CoV-2, with this number expected to grow even higher prior to the widespread availability of vaccines (Moscola et al 2020).

Following the second dose, GMT further increased for both SDSD + LDSD Immunogenicity analysis set, and the SDSD Immunogenicity analysis set (see Table 31 at the Summary of Clinical Efficacy). This increased response following the second dose was consistent across assays for nAb (pseudoneutralisation) [see Table 33 of the Summary of Clinical Efficacy] and

live nAb [see Immuno Tables 1.7.1.3.1 and 1.7.1.3.2, Module 5.3.5.3) and anti-RBD (see Immuno Tables 1.7.1.2.1 and 1.7.1.2.2, Module 5.3.5.3).

4.2.8.3 Humoral Immune Response by Subcategories

A strong induction of humoral immunogenicity, as measured by anti-S, anti-RBD, and nAb to SARS-CoV-2, was observed following the first dose and the second dose of AZD1222 for all the subgroups of comorbid conditions at baseline, country, and age at screening. The rate of seroconversion after the first dose and the second dose was consistent with the overall Immunogenicity Analysis Set for all subgroups. Observations for S-binding antibody and nAb (pseudoneutralisation) levels for each subgroup category are described below.

Adults with Comorbid Conditions at Baseline

At DCO2, no differences in immunogenicity were observed in the subcategory of participants with comorbidity compared with those without comorbidity, when examining binding antibody (see Table 31 of the Summary of Clinical Efficacy) and nAb GMTs (see Table 33 of the Summary of Clinical Efficacy) after both the first dose and second dose. Responses analysed in a live neutralisation assay confirmed this finding, with GMTs = 176.28, 594.70 AU/mL after first and second dose of AZD1222 in the SDSD + LDSD analysis set with no comorbidity, and GMT = 170.60, 516.65 AU/mL in the SDSD + LDSD analysis set with comorbidity at baseline (see Immuno Tables 2.7.1.3.1.a and 2.7.1.3.1.b, Module 5.3.5.3). These results were consistent with data reported for DCO1.

Country

Similar levels of S-binding antibody were induced after the first dose in UK, Brazil, and South Africa (see Table 31 of the Summary of Clinical Efficacy) in the SDSD analysis set where comparisons may be best drawn due to the use of this dose level in all countries. Following the second dose, GMT for S-binding antibodies further increased for each country, although the GMT observed in Brazil was numerically lower compared with the UK and South Africa. Pseudoneutralisation data were similarly lower following the second dose in the Brazilian participants (see Table 33 of the Summary of Clinical Efficacy). Comparisons between UK and Brazil may be confounded by dose interval (see Section 4.2.9.1 and Supplemental Tables IEMT 193.1.1.2.a, 193.1.1.2.b, 193.1.1.2.c, and 193.1.1.2.e, Module 5.3.5.3). The nAb titres by pseudoneutralisation in South Africa were high; however, these data must be interpreted with caution, due to the low numbers of study participants analysed at the point of data cut-off.

Older Adults (≥ 65 years of age)

At DCO2, in the SDSD Immunogenicity Analysis Set (all participants ≥ 65 years of age received SDSD), the GMT for S-binding antibodies were numerically lower in adults

≥ 65 years of age than in younger adults after both the first dose and second dose (see Table 31 of the Summary of Clinical Efficacy). Similarly, nAb (pseudoneutralisation) GMTs were lower in the older adults (see Table 33 of the Summary of Clinical Efficacy).

Published data of immune response in healthy older adults suggested that immunogenicity by binding antibody and nAb responses were not numerically different from younger adults (Ramasamy et al 2020). Data presented in this submission differ in both the validated assays that have been utilised, as well as the sample size, which is larger and draws from a broader population also including older adults with comorbidities. Furthermore, the majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the numerically lower titres observed (see discussion in Section 4.2.9.1). To address the potential confounder of dose interval, anti-S binding responses for study participants within the SDSD Seronegative for Efficacy Analysis Set were stratified by both age and dose interval. Median titres were lower for older adults overall; however, at dose intervals of ≥ 4 weeks to < 8 weeks, responses in adults ≥ 65 years of age were more similar to those of adults 18-64 years of age. This was observed for anti-S binding responses, and neutralising antibody titres as determined by a pseudoneutralisation assay or a live neutralisation assay (see Section 4.1.5.3, Module 2.7.2).

4.2.9 Exploratory Analyses of Dose and Regimen

The studies contributing to the pooling were not designed to investigate dose level and regimen. However, discrepant determination of product concentration between early analytical methods used led to the fact that some participants received a lower dose than planned. Also, delays in the second dose associated with product unavailability related to the rapid conditions in which the trials were initiated, while the scale up of manufacturing was ongoing, led to the fact that participants received the second dose over a range of time intervals.

In this section, the results of an exploratory analysis of the pooled data set for efficacy is presented to assess the effect of dose interval on vaccine efficacy. Data previously presented (included in the original submission) have shown that the difference in vaccine efficacy observed for participants who received LDSD was primarily due to longer dose intervals, and therefore no further analyses of dose level have been conducted at DCO2.

4.2.9.1 Effect of Dose Interval on Efficacy

The contribution of the interval between doses on the immune response of a 2-dose schedule of AZD1222 has been explored in the dataset. Spike-binding antibody titres after the first and second doses were analysed by dose interval for SDSD and LDSD (Table 17). For the SDSD group, after starting from similar immune responses to the first dose there is a clear trend that longer dose intervals are associated with higher responses induced by the second dose. The same pattern is reflected in the nAb responses as determined by pseudoneutralisation assay (Table 18). The GMT values for the shortest dose interval, < 4 weeks, are also high. However,

these data must be interpreted with caution given the small number of participants and the wide confidence intervals in this subgroup.

Taken together, these data strongly suggest that longer dose intervals are associated with higher levels of immunogenicity.

Table 17 Quantification of SARS-CoV-2 Spike Antibody Levels by Dosing Interval (SDSD Immunogenicity Analysis Set, Seronegative at Baseline)

		SDSD			
		AZD1222			
		< 4 wks	≥ 4 to < 8 wks	≥ 8 to < 12 wks	> 12 wks
Visit Window	Statistic	N = 32	N = 815	N = 587	N = 272
Baseline	N	31	691	560	256
	GMT	**62.36**	**60.02**	**54.12**	**55.40**
	95% CI for GMT	(37.9, 102.7)	(54.7, 65.9)	(49.4, 59.3)	(48.0, 64.0)
Day 28 post the first dose	N	32	665	513	256
	GMT	**13523.33**	**8003.77**	**8681.29**	**8162.34**
	95% CI for GMT	(8968.3, 20391.9)	(7323.5, 8747.2)	(7866.4, 9580.6)	(7098.4, 9385.7)
Day 28 post the second dose	N	30	672	553	256
	GMT	**28940.42**	**22069.86**	**35258.11**	**53475.18**
	95% CI for GMT	(20505.2, 40845.7)	(20578.3, 23669.6)	(32712.7, 38001.5)	(47719.1, 59925.6)

Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention.
Titer values measured as below LLoQ (33) are imputed to a value that is half of the LLoQ. Titer values measured as above ULoQ (2000000) are imputed at the ULoQ value.
Participants with indeterminate and missing value of baseline serostatus are not included.
S = Spike, GMT = Geometric Mean Titer, CI = Confidence Interval, LLoQ = Lower Limit of Quantification, ULoQ = Upper Limit of Quantification, NE=Not Evaluable.
Sources: Supplemental Tables IEMT 193.1.1.2.a, 193.1.1.2.b, 193.1.1.2.c, 193.1.1.2.e, Module 5.3.5.3.

Table 18 Quantification of nAbs (by Pseudoneutralisation Assay) Levels by Dosing Interval (SDSD Immunogenicity Analysis Set, Seronegative at Baseline)

		SDSD			
		AZD1222			
		< 4 wks	≥ 4 to < 8 wks	≥ 8 to < 12 wks	> 12 wks
Visit Window	Statistic	N = 32	N = 815	N = 587	N = 272
Baseline	N	20	396	195	127
	GMT	**23.766**	**20.662**	**20.291**	**20.000**
	95% CI for GMT	(16.56, 34.10)	(19.99, 21.35)	(19.72, 20.88)	(NE, NE)
Day 28 post the first dose	N	18	352	172	110
	GMT	**189.084**	**53.856**	**68.915**	**64.028**
	95% CI for GMT	(100.67, 355.16)	(47.26, 61.38)	(56.72, 83.72)	(49.56, 82.71)
Day 28 post the second dose	N	17	356	182	121
	GMT	**326.744**	**130.936**	**215.953**	**272.323**
	95% CI for GMT	(207.22, 515.22)	(115.22, 148.79)	(187.10, 249.25)	(219.92, 337.22)

Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention.
Titer values measured as below LLoQ (40) are imputed to a value that is half of the LLoQ. Titer values measured as above ULoQ (787339) are imputed at the ULoQ value.
Participants with indeterminate and missing value of baseline serostatus are not included.
NAb = Neutralizing Antibody, GMT = Geometric Mean Titer, CI = Confidence Interval, LLoQ = Lower Limit of Quantification, ULoQ = Upper Limit of Quantification, NE=Not Evaluable.
Source: Supplemental Tables IEMT 193.1.4.2.a, 193.1.4.2.b, 193.1.4.2.c, 193.1.4.2.e, Module 5.3.5.3.

At DCO2, the vaccine efficacy has been analysed by similar dose intervals for the SDSD + LDSD, and the SDSD seronegative for efficacy analysis set (Table 19). In both analysis sets, the trend for increased vaccine efficacy with longer dose intervals is consistent with what would be expected based on observed immunogenicity associated with longer dose intervals. With additional cases and participants in DCO2, the data is still consistent with reports from DCO1.

Table 19 Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose in the Pooled Analysis Set by Time Interval Between Doses (COV001 + COV002 + COV003 + COV005), DCO2 (07 December 2020)

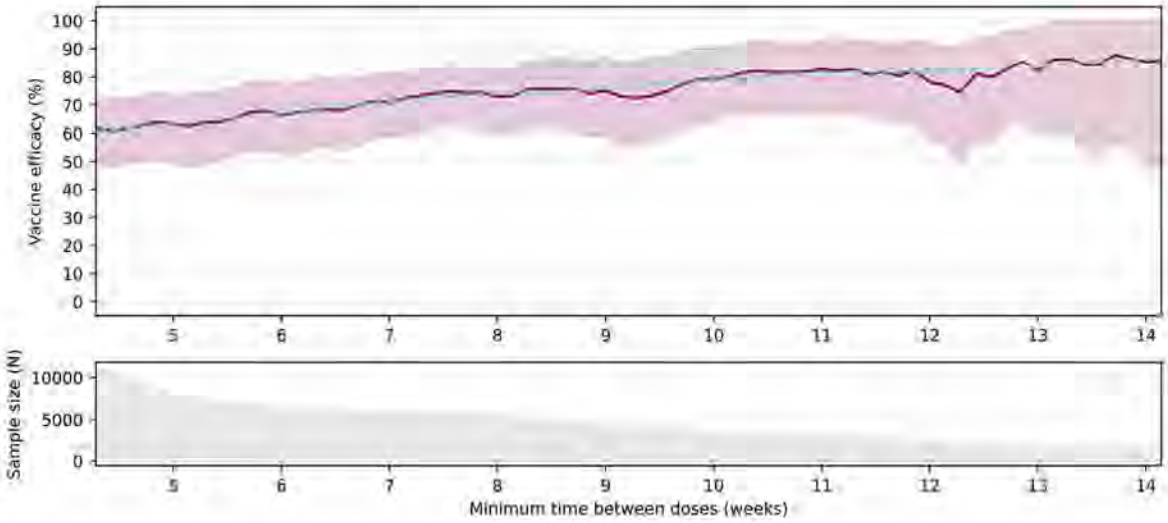
Analysis set Time interval between Dose 1 and Dose 2	Participants with events AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD + LDSD Seronegative for Efficacy Analysis Set					
< 4 weeks	1 / 206 (0.49)	3 / 203 (1.48)	66.56	(-221.83, 96.53)	0.343
≥ 4 to < 8 weeks	47 / 4312 (1.09)	90 / 4200 (2.14)	50.48	(29.56, 65.19)	<0.001
≥ 8 to ≤ 12 weeks	23 / 2308 (1.00)	92 / 2348 (3.92)	74.97	(60.48, 84.14)	<0.001
> 12 weeks	13 / 1771 (0.73)	63 / 1830 (3.44)	78.91	(61.68, 88.39)	<0.001
< 6 weeks	35 / 3905 (0.90)	76 / 3871 (1.96)	55.09	(32.99, 69.90)	<0.001
≥ 6 to 8 weeks	20 / 1124 (1.78)	44 / 1023 (4.30)	59.72	(31.68, 76.25)	<0.001
9 to 11 weeks	14 / 1530 (0.92)	52 / 1594 (3.26)	72.25	(49.95, 84.61)	<0.001
≥ 12 weeks	15 / 2038 (0.74)	76 / 2093 (3.63)	79.99	(65.20, 88.50)	<0.001
SDSD Seronegative for efficacy analysis set					
< 4 weeks	1 / 206 (0.49)	3 / 203 (1.48)	66.56	(-221.83, 96.53)	0.343
≥ 4 to < 8 weeks	47 / 4294 (1.09)	90 / 4183 (2.15)	50.48	(29.55, 65.19)	<0.001
≥ 8 to ≤ 12 weeks	18 / 1555 (1.16)	66 / 1580 (4.18)	72.64	(53.95, 83.75)	<0.001
> 12 weeks	8 / 1146 (0.70)	38 / 1213 (3.13)	77.62	(51.98, 89.57)	<0.001
< 6 weeks	35 / 3890 (0.90)	76 / 3856 (1.97)	55.10	(33.00, 69.91)	<0.001
≥ 6 to 8 weeks	20 / 1112 (1.80)	44 / 1009 (4.36)	59.92	(32.01, 76.37)	<0.001
9 to 11 weeks	11 / 906 (1.21)	32 / 958 (3.34)	63.65	(27.96, 81.66)	0.004
≥ 12 weeks	8 / 1293 (0.62)	45 / 1356 (3.32)	81.31	(60.31, 91.20)	<0.001

VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade ≥ 4.

Source: Supplemental Tables IEMT 142.1.1.1.1, 142.1.1.1.2, 142.1.1.1.3, 142.1.1.1.4, 142.1.1.2.1, 142.1.1.2.2, 142.1.1.2.3, and 142.1.1.2.4; Supplemental Tables IEMT 143.1.1.1.1, 143.1.1.1.2, 143.1.1.1.3, 143.1.1.1.4, 143.1.1.2.1, 143.1.1.2.2, 143.1.1.2.3, and 143.1.1.2.4, Module 5.3.5.3.

The effect of dose interval on vaccine efficacy has been further explored in the SDSD + LDSD, and the SDSD analysis population. Participants were removed progressively from the dataset in sequence, from patients with the shortest dose intervals to those with the longest, and efficacy was recalculated at every point in those that remained. The minimum dose interval required to remain in the dataset was iteratively increased from 30 days to 100 days, one day at a time. This is equivalent to performing 70 subgroup analyses in a sequence, where the included subgroup shrinks each time and the median and minimum dose interval progressively increase. To approximate the uncertainty, 1000 bootstrapping iterations (random resampling with replacement) were performed with each filtered dataset, and summarised vaccine efficacy across those samples. Results for the SDSD Seronegative for Efficacy Analysis Set are shown in Figure 10 (for the SDSD + LDSD Seronegative for Efficacy Analysis Set, see Figure 14 in the Summary of Clinical Efficacy). The solid red line corresponds to the median vaccine efficacy for each point, the dashed blue line is a smoothed version of the median line, and the shaded region corresponds to the empirical 95% CI. Below the plots of median vaccine efficacy for dose interval, the number of participants contributing to the analysis at each calculation is shown graphically. After approximately 12 weeks, CIs widen as the sample sizes become smaller, and the trend should be interpreted with more caution. The minimum dosing interval in these studies was 4 weeks.

Figure 10 Exploratory Analysis of Median Vaccine Efficacy for Dose Interval (SDSD Seronegative for Efficacy Analysis Set)



Source: data on file.

4.2.9.2 Protection after First Dose

An ad hoc analysis was conducted to determine whether protective immunity was induced by the first dose (Table 20). The follow-up time began at 22 days after the first dose and was censored at the time of the second dose; participants who had not received a second dose were censored at the time of the data cut-off, discontinuation, or COVID-19 event. For those participants who had SD as their first dose, vaccine efficacy was demonstrated between 22 days after dose 1 through the second dose at a level similar to that seen after the complete SDSD dosing regimen (66.73%, 95% CI: 57.41%, 74.01%; Table 8). Over the subsequent 12 weeks Cumulative Incidence plots show divergence, but the amount of data is very limited past this point (Figure 11). This indicates that the first SD dose provides protective immunity and that this would offer protection until the second dose is administered up to 12 weeks duration.

Table 20 Vaccine Efficacy for Incidence of First SARS CoV 2 Virologically confirmed Symptomatic COVID 19 Occurring ≥22 days Post First Dose and Before Second Dose

	Participants with events						
	AZD1222		Control		VE (%)	95% CI	P-value
Analysis set [a]	N	n (%)	N	n (%)			
Dose 1 SD	9335	32 (0.34)	9312	82 (0.88)	60.99	(41.37, 74.05)	<0.001
Dose 1 LD	1704	19 (1.12)	1703	14 (0.82)	-35.63	(-192.35, 35.52)	0.488

[a] Includes participants who were seronegative at baseline.

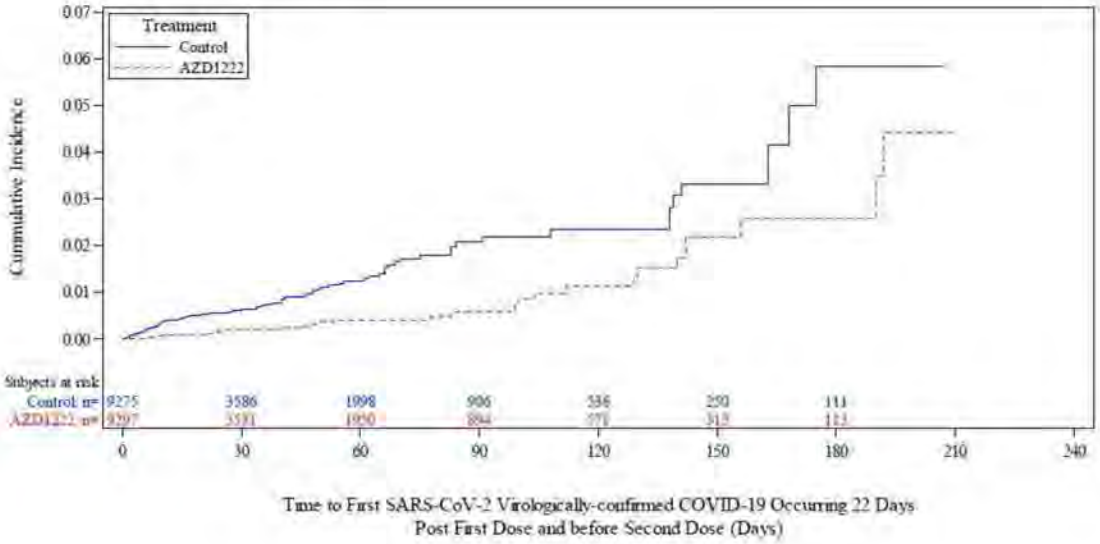
VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the terms of study code and age group at screening (18-55 years, 56-69 years, and ≥70 years) as covariates, as well as the log of the follow-up time as an offset.

VE was defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

The follow up time beginning 22 days post 1st dose and before 2nd dose, or event, or discontinuation, or data cut-off, whichever is earliest. Participants who only received their first dose are also included in the analysis until event, discontinuation or data cut-off, whichever is earlier.

Source: Supplemental Tables IEMT157.7 .2 and IEMT252.1, Module 5.3.5.3.

Figure 11 **Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed COVID-19 Occurring Post First Dose + 22 Days and Before Second Dose of Study Intervention (Dose 1 SD Seronegative for Efficacy Analysis Set)**



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose + 22 days before second dose of study intervention, in days, has been calculated as follows: Date of first SARS-CoV-2 virologically confirmed test occurring 22 days post first dose before second dose –(date of first dose of study intervention +22) +1.
The observation period for the endpoint was 22 days post first dose up to 1 year in study.
COVID-19 endpoints were based on adjudicated events.
Source: Supplemental Figures IEMT220.1, Module 5.3.5.3.

.

4.3 Efficacy Conclusions

At the time of DCO2, the primary efficacy analysis was conducted with 17178 participants in the pooled efficacy population with a median follow-up of ≥ 68 days days after Dose 2. A two-dose regimen of AZD1222 was found to be 66.73% (95.84% CI: 57.41%, 74.01%) efficacious against symptomatic COVID-19. This analysis of the primary endpoint met the statistical criterion of success as the lower bound of the CI was > 20% and exceeded the more stringent criterion of >30%. Complete protection against COVID-19 hospital admission (WHO Severity Grading ≥ 4) was shown ≥ 22 days after the first dose of AZD1222 SD (0 vs 14 cases in Control group, of which two were severe, one with a fatal outcome). There was a similar level of vaccine efficacy by country for the UK and Brazil, whilst in South Africa there were too few cases to allow a firm conclusion from this dataset. For the SDSD regimen, protection begins approximately 22 days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a time interval between 4 to 12 weeks with demonstrated good interdose protection.

The vaccine was highly immunogenic; after a single dose of SD or LD seroconversion of S-binding antibody was >98%. Seroconversion of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Increasing the dose interval between first and second dose resulted in increases in both binding and neutralising antibody responses. Consistent with this, there is a clear trend towards an increase in vaccine efficacy with increased dose interval up to 12 weeks.

Adults with pre-existing comorbidity showed similar vaccine efficacy and immune responses when compared to the general population. Whilst older adults (≥ 65 years) experienced a small number of events, which does not allow a precise determination of vaccine efficacy, vaccine efficacy data are consistent with the general population. Rates of seroconversion to binding and live neutralising antibody titres were similar to younger adults. However, their absolute titres of binding and neutralising antibody were numerically lower, which may be confounded by dose interval (Section 4.2.8.3). The clinical significance of this observation is currently unknown.

Taken in its entirety, the efficacy and immunogenicity data support the use of an AZD1222 vaccine regimen consisting of two standard doses (SDSD) given between 4 and 12 weeks apart that offers benefit to the adult population, including those with comorbidity and those above 65 years of age.

A more recent analysis of the COV005 study from South Africa by Madhi and colleagues (Madhi et al 2021), using an unlocked dataset, showed limited vaccine efficacy against mild disease caused by the B.1.351 variant. However, no determination of effect against severe disease or hospitalization was shown, since the population analysed consisted mainly of young healthy adults (median age: 31 years old) with no events in these categories. It is believed that

protection against severe disease and hospitalizations will still be achieved with this vaccine against the B.1.351 variant, as levels of nAbs were equivalent to other vaccines that protect against severe disease, particularly likely when dose interval is optimized to 8-12 weeks. Further, T cell responses may not be as severely affected by the point mutations in the variant strains, and may therefore provide unaffected protection against severe disease.

Additionally, a recent report by Emary and colleagues (Emary et al 2021) showed that efficacy of ChAdOx1 nCoV-19 against the B.1.1.7 variant of SARS-CoV-2 is similar to the efficacy of the vaccine against other lineages.

Since DCO1, there was an increase in the number of participants included in the primary endpoint analysis, as well as the number of COVID-19 cases, and there were more participants with longer follow-up. Moreover, with the inclusion of COV005 in the efficacy analyses, the racial diversity of the study population has increased. The number of participants $\geq$ 65 years at baseline has also increased. Overall, the efficacy data from DCO2 were consistent with DCO1, with more cases and participants, thus increasing the robustness of the vaccine data.

5 OVERVIEW OF SAFETY

Safety data from the interim pooled safety analysis (DCO1, 04 November 2020) have previously been submitted. This Clinical Overview presents and discusses further key safety data from the pooled safety analysis. The DCO date for the analyses included in this summary was 07 December 2020 (DCO2). All data outputs from the pooled analyses are provided in Module 5.3.5.3. Results of this pooled analysis are being provided as further evidence of the safety of the AZD1222 vaccine. The safety of AZD1222 has been evaluated for multiple dosing regimens, by country, as well as in high-risk adult populations of older adults and adults with comorbidities, who have an increased risk of death or severe disease associated with COVID-19.

5.1 Safety Experience with ChAdOx1 Viral Vector Vaccines

Replication deficient viral vectors have been investigated for a variety of vaccine applications due in part to their favourable safety profiles, and replication deficient adenovirus vectored vaccines have an established safety profile, having been administered in thousands of people, including infants, children, elderly, and immunosuppressed individuals. Replication deficient chimpanzee adenoviruses have been specifically developed as viral vaccine vectors due to concerns that human adenovirus use as a vaccine vector could be limited due to pre-existing prevalence of neutralising antibodies in humans. In addition to AZD1222, the ChAdOx1 platform has been used to develop experimental prophylactic candidate vaccines for influenza, tuberculosis, malaria, chikungunya, Zika, MERS-CoV, hepatitis B, and capsular group B meningococcus and experimental therapeutic vaccines for prostate cancer and HIV. All of

these experimental vaccines are currently being tested in clinical trials. Supportive safety data are provided from publicly available results from vaccine clinical development programmes that are using the ChAdOx1 vaccine vector.

Currently, results with the ChAdOx vector are available from clinical studies investigating influenza (Antrobus et al 2014, Coughlin et al 2018), chikungunya (Folegatti et al 2019), tuberculosis (Wilkie et al 2020), prostate cancer (Cappuccini et al 2020, Tuthill et al 2020), and Middle East respiratory syndrome (Folegatti et al 2020a). In a study investigating tuberculosis, with safety follow-up of 24 weeks for 12 participants, 32 weeks for 12 participants and 41 weeks for 12 participants, there were no SAEs reported in any group (Wilkie et al 2020). Among unsolicited events during this long-term follow-up, 9 haematological AEs that were considered related to ChAdOx vaccine were reported, all mild to moderate in severity and all resolved fully with exception of a moderate lymphopaenia considered possibly related. In a study of 23 patients with prostate cancer and 6 months of follow-up, the authors report there were no Grade 4 or 5 AEs and the only Grade 3 AE was a chest infection which was not thought to be related to treatment (Tuthill et al 2020). In a study with a vaccine against MERS, 24 participants that received the ChAdOx vectored vaccine were followed up for 6 months and with 19 of them having 12 months follow-up (Folegatti et al 2020a). There were no serious adverse drug reactions and only 1 SAE reported which was judged not related to treatment. A majority of AEs was mild or moderate in severity and all resolved within the follow-up period of 12 months.

Overall, available data from studies with other ChAdOx1 vectored vaccine candidates demonstrate the vector is well tolerated at all dose levels investigated, with no SAEs related to the vaccine reported. Local and systemic AEs were predominantly self-limiting and short-lived. These vaccines demonstrated robust immunogenicity after a single dose and favourable safety profiles.

5.2 Safety Data Collection and Analysis

The assessment of AZD1222 safety included in this document is based on the primary analysis of the pooled results from 4 ongoing University of Oxford-sponsored studies (Study COV001, Study COV002, Study COV003, and Study COV005), as of DCO2 of 07 December 2020. Pooling was deemed appropriate as the studies had similar inclusion/exclusion criteria, safety endpoints, and frequency of assessments. The control groups, which include both the MenACWY active control (dose 1 and 2 in studies COV001 and COV002 and dose 1 in study COV003) and a saline placebo control (dose 2 in Study COV003 and dose 1 and 2 in Study COV005), were pooled together. As a result, reactogenicity can be expected to be somewhat reduced in the control group compared to the AZD1222 group, in which all participants received active treatment.

Safety was assessed in all studies by evaluation of solicited AEs commonly associated with vaccinations, unsolicited AEs, SAEs (including deaths) and AESIs. Biochemistry and haematology clinical laboratory tests were also evaluated for a subset of participants in Studies COV001, COV002, and COV005.

Solicited AEs were collected via diary card in a subset of participants for 7 days following each vaccination. As there were differences across studies related to how solicited events were collected and severity graded in patient diaries, a mapping and pooling strategy was developed for pooling these events (see Appendix B of the MAA SAP, Edition 7). Unsolicited AEs from the start of each dose through 28 days (ie, day of vaccination and the following 27 days) were also summarised for all participants. All unsolicited AEs were coded to preferred term using MedDRA Version 23.1 and pooled directly. For laboratory values, all data were graded for severity using the FDA toxicity grading scale (see Appendix B of the MAA SAP, Edition 7), and the most extreme result reported in the 28 days post-dose period is presented. Participants were analysed according to actual treatment received.

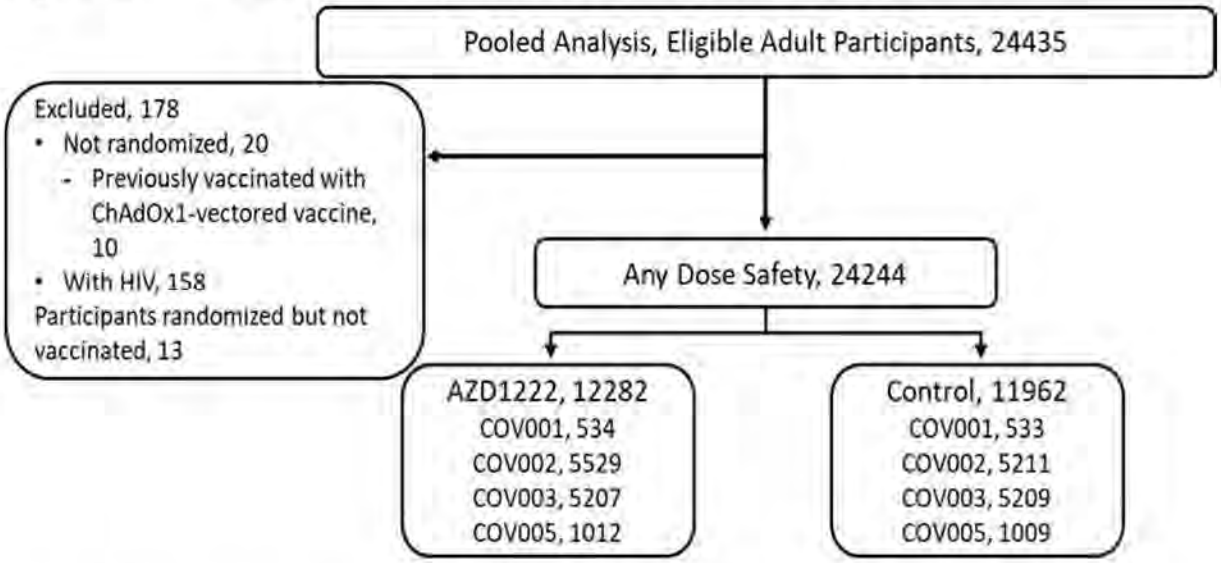
SAEs and AESIs were summarised for all participants throughout the study period (following last vaccination up to the cut-off date). Pre-specified AESIs for AZD1222 were developed in consultation with the US FDA and in line with MHRA guidance and included neurologic, vascular, haematologic, and immunologic events (see Table 9 of the MAA SAP, Edition 6, Module 5.3.5.3). For narratives for related SAEs, related AESIs ≥ Grade 3, deaths, and SAEs due to COVID-19, see Safety Narratives, Module 5.3.5.3.

Solicited and unsolicited AEs, SAEs, and AESIs were reviewed using the Any Dose for Safety Analysis Set. These safety parameters were also reviewed by subgroup for age at randomisation, country, comorbidity at baseline, and baseline serostatus. Incidences of solicited AEs and unsolicited AEs were established by using the Dose 1 SD for Safety Analysis Set, defined as participants who received SD as their first dose, in order to match the proposed dosing. An analysis of participants who received LD as their first dose or were in the corresponding control group was also conducted.

5.3 Clinical Safety Database: Exposure and Demography

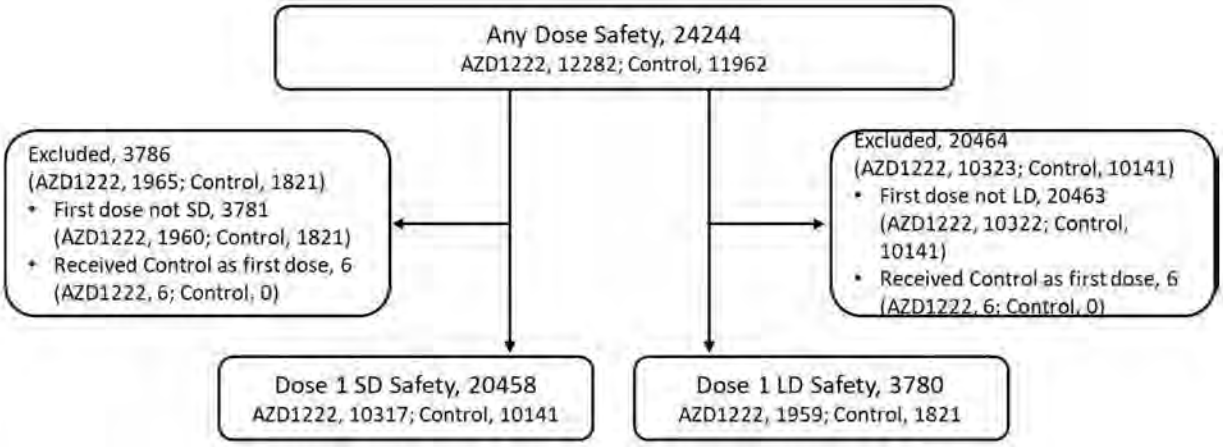
In the Any Dose for Safety Analysis Set, there are a total of 24244 participants who received at least 1 dose of study intervention by DCO2, including 12282 in the AZD1222 group and 11962 in the control group. The disposition of participants in the pooled analysis sets for safety is provided in Figure 12 and Figure 13.

Figure 12 Participant Disposition (AZD1222, Pooled Analysis)



Eligible participants included participants who signed informed consent and were not screen failures.
ChAdOx1 = chimpanzee adenovirus ox1; HIV = human immunodeficiency virus.
Source: Main Safety Tables 1.1.1.1 and 1.1.2.1, Module 5.3.5.3.

Figure 13 Participant Disposition, Safety Analysis Sets (AZD1222, Pooled Analysis)



Reasons for exclusion may not be mutually exclusive.
Source: Main Safety Table 1.1.1.1, Module 5.3.5.3.

In the Any Dose for Safety Analysis set, the median number of days of exposure was similar between the AZD1222 treatment group (140.0 days) and the control group (139.0 days) following the first dose. The median exposure in the Dose 1 SD Safety analysis set was

80.0 days in the AZD1222 group and 79.0 days in the control group, following the second dose. The median exposure in the Dose 1 SD Safety analysis set was 119 days in the AZD1222 group and 118 days in the control group and 74 days each following the second dose in the AZD1222 treatment group and control group. (see Supplemental Table IEMT 204.1.1a, 204.1.2a, Module 5.3.5.3).

The two-dose study intervention regimen was received by more than three-quarters of participants in the AZD1222 group (85.1%) and control group (85.3%) at the time of data cut-off (Table 7). Overall, approximately 50% of the participants had a dose interval < 6 weeks (50.7% for AZD1222 group, and 50.2% for the control group) (see Main Safety Table 1.2.1.1, Module 5.3.5.3).

Most of the participants were 18 to 64 years of age (90.6%), with 9.4% of participants age 65 years or older. Overall, in the safety population, 55.7% were female, 44.3% were male, 75.6% were White, 9.9% were Black, 4.4% were mixed race, 3.5% were Asian, and 6.5% were reported to be of other races (see Main Safety Table 1.1.3.1, Module 5.3.5.3). Over a third of participants (36.5% in the AZD1222 group and 36.7% in the control group) had a comorbidity at baseline. The demographic and baseline characteristics were generally similar among participants that received AZD1222 and the control treatments.

The studies excluded pregnant/breastfeeding women at enrolment , participants with severe immunodeficiency, or participants with severe underlying disease. A subset of participants with HIV diagnosed at study start were included in COV002 and COV005; however, these participants were excluded from the pooled analysis.

5.4 Safety Profile of AZD1222

5.4.1 Common Adverse Events

5.4.1.1 Solicited Adverse Events

In the Dose 1 SD for Safety Analysis Set, 2725 participants in the AZD1222 group and 2573 participants in the control group were evaluated for solicited AEs within 7 days after at least 1 vaccination. Solicited local injection site and systemic AEs were reported by 73.5% and 73.1% of evaluated participants, respectively, within the first 7 days following any vaccination with AZD1222. In the control group, solicited local injection site and systemic AEs were reported by 48.3% and 60.2% of participants, respectively (Table 21).

For frequencies of individual solicited local and systemic AE terms for the Dose 1 SD for Safety Analysis set, see Main Safety Tables 1.5.1.2.2 and 1.5.1.3.2. In the Dose 1 SD for Safety Analysis Set, the most frequently reported solicited local injection site AEs within 7 days after either vaccination with AZD1222 were tenderness (63.8% vs 40.1% in control) and pain (54.3% vs 37.5% in control). Other solicited local injection site AEs reported in ≥ 10% of AZD1222 participants were warmth (17.9% vs 15.2% in control), itch (13.1% vs 7.8% in

control), and bruising (17.9% vs 6.7% in control) (see Main Safety Tables 1.5.1.2.2, Module 5.3.5.3). In the Dose 1 SD for Safety Analysis Set, the most frequently reported solicited systemic AEs within 7 days after either vaccination with AZD1222 were fatigue (53.0% vs 38.6% in control) and headache (52.7% vs 39.8% in control); other frequently reported systemic solicited AEs were muscle pain (43.9% vs 22.3% in control), malaise (44.4% vs 21.0% in control), feverishness, (33.5% vs 11.0% in control), chills (32.2% vs 8.4% in control), joint pain (26.6% vs 13.0% in control), nausea (22.2% vs 13.4% in control), and fever (7.6% vs 1.5% in control) (see Main Safety Table 1.5.1.3.2, Module 5.3.5.3).

Most of the solicited local and systemic AEs following vaccination with AZD1222 were mild to moderate in severity, with only 1.9% of patients reporting solicited local AEs and 8.4% of patients reporting solicited systemic AEs that were of grade 3 severity or greater.

Solicited local and systemic AEs were reported less frequently after the second vaccination than after first vaccination of AZD1222; overall, solicited local and systemic AEs were reported by 46.0% and 44.4% of evaluated participants after the second vaccination compared with 69.3% and 69.5% of evaluated participants after the first vaccination (see Main Safety Table 1.5.1.1.2, Module 5.3.5.3). When compared with the first dose, adverse reactions reported after the second dose were generally milder.

Reactogenicity of AZD1222 was highest on Day 1, the day following vaccination; solicited local injection site and systemic events were reported by 63.4% and 60.8% of participants, respectively, on Day 1 following any vaccination with AZD1222; by Day 2, solicited local injection site and systemic events were reported by 53.8% and 38.7% of participants, respectively (see Safety Tables 1.5.1.4.2 and 1.5.1.5.2, Module 5.3.5.3). By Day 7, the overall incidence of participants with at least 1 solicited local or systemic event was 3.8% and 13.9%, respectively. The incidence of participants reporting individual solicited local injection site and systemic AEs decreased to $\leq$ 2% for most of the individual events by Day 5 to 7, indicating that these events were self-limiting and of shorter duration. The majority of the events reported on Day 7 were mild or moderate in severity.

Table 21 Overall Summary of Solicited Adverse Events Collected Within 7 Days After Vaccination: Pooled Analysis (Dose 1 SD for Safety Analysis Set)

	Days 0 to 7 After Any Vaccination		Days 0 to 7 After First Vaccination		Days 0 to 7 After Second Vaccination	
	AZD1222 (N = 10317)	Control (N = 10141)	AZD1222 (N = 10317)	Control (N = 10141)	AZD1222 (N = 10317)	Control (N = 10141)
Evaluated for solicited AEs, n	2725	2573	2664	2503	1926	1799
Any solicited AE, n (%)	2332 (85.6)	1835 (71.3)	2199 (82.5)	1642 (65.6)	1177 (61.1)	847 (47.1)
Any solicited local AE, n (%)	2002 (73.5)	1244 (48.3)	1845 (69.3)	1094 (43.7)	886 (46.0)	498 (27.7)
Any ≥ Grade 3 severity solicited local AE, n (%)	52 (1.9)	19 (0.7)	38 (1.4)	14 (0.6)	18 (0.9)	7 (0.4)
Any solicited systemic AE, n (%)	1991 (73.1)	1548 (60.2)	1851 (69.5)	1342 (53.6)	855 (44.4)	648 (36.0)
Any ≥ Grade 3 severity solicited systemic AE, n (%)	229 (8.4)	67 (2.6)	197 (7.4)	41 (1.6)	40 (2.1)	32 (1.8)

Participants with multiple events in the same category were counted once in that category. Participants with events in more than 1 category were counted once in each of those categories. Denominators used in the percentage calculations were the number of participants "evaluated for solicited AEs".
Solicited AEs were assessed daily after vaccination for Day 0 to Day 6 for COV005 and to Day 7 for rest of studies.
No grade 4 severity option for events collected in COV005. Pain and Warmth, Malaise, Nausea and Vomiting were not assessed for COV005. Induration did not include COV005 as the grading scale was not compatible. Feverishness and Chills did not include COV005 since no severity grading collected. For Redness, Swelling and Fever severity grading was derived based on reported value. Bruising only collected for COV005.
AE = adverse event; NC = not calculated; SD = standard dose
Source: Main Safety Table 1.5.1.1.2, Module 5.3.5.3

5.4.1.2 Unsolicited Adverse Events

In the Any Dose for Safety Analysis Set, 41.8% of participants in the AZD1222 group and 31.6% of participants in the control group reported an unsolicited AE within 28 days following any vaccination (see Main Safety Table 1.5.2.1.1, Module 5.3.5.3). In the AZD1222 group, there were 35.1% of participants with an unsolicited AE within 28 days of the first vaccination and 13.8% of participants within 28 days of the second vaccination. A majority of the unsolicited events were mild to moderate in severity; the incidence of events with ≥ Grade 3 severity was 2.1% of participants in the AZD1222 group and 1.7% of participants in the control group (see Main Safety Table 1.5.2.1.1, Module 5.3.5.3). In the AZD1222 group, there were 1.5% of participants with an unsolicited AE with ≥ Grade 3 severity within 28 days of the first vaccination and 0.6% of participants with an unsolicited AE with ≥ Grade 3 severity within 28 days of the second vaccination.

For participants in the Dose 1 SD for Safety Analysis Set, the most common unsolicited AEs were consistent with AEs commonly observed following vaccination (Table 22). Vaccination site pain was the most commonly reported event in both AZD1222 and control groups. A numerically higher incidence in the most common unsolicited AEs was observed in the AZD1222 group compared with the control group, which could be attributed at least in part due to the proportion of participants that received saline placebo treatment in the control group. For unsolicited AEs reported after ≤7 days after any vaccination and > 7days after any vaccination, see Main Safety Table 1.5.2.6.1, 1.5.2.7.1, 1.5.2.11.1, and 1.5.2.12.1, Module 5.3.5.3. The most common AE reported in the SOC of Nervous system disorder in Dose 1 SD Safety Analysis Set is Headache (AZD1222: 1278 [12.4%]; Control: 872 [8.6%]) and the majority of the events of headache were considered as related by the investigator (see Main Safety Tables 1.5.2.2.2 and 1.5.2.5.2, Module 5.3.5.3).

Table 22 Unsolicited Adverse Events within 28 Days After Dose (≥ 2% in Either Treatment Group) by PT: Pooled Analysis (Dose 1 SD for Safety Analysis Set)

	Number (%) of Participants [a]	
PT (MedDRA version 23.1)	AZD1222 (N = 10317)	Control (N = 10141)
Vaccination site pain	1471 (14.3)	902 (8.9)
Headache	1278 (12.4)	872 (8.6)
Myalgia	1031 (10.0)	425 (4.2)
Pyrexia	982 (9.5)	246 (2.4)
Fatigue	565 (5.5)	352 (3.5)
Chills	470 (4.6)	119 (1.2)
Asthenia	315 (3.1)	172 (1.7)
Malaise	302 (2.9)	167 (1.6)
Nausea	236 (2.3)	149 (1.5)

[a] Number (%) of participants with AEs, sorted on international order for SOC and alphabetical order for PT. Participants with multiple events in the same PT were counted only once in each of those PTs. Participants with events in more than 1 PT are counted once in each of those PTs.

Unsolicited AEs collected from the start of each dose through 28 days, SAE and AESI collected from first dose to 364 days after the last vaccination were summarized.

Source: Main Safety Table 1.5.2.3.2, Module 5.3.5.3.

In addition to the unsolicited AEs shown using a 2% cut-off (Table 22), the AEs shown in Table 23 were considered to have a reasonable possibility of a causal association with AZD1222, based on an overall assessment of data from all the pooled data studies, as well as of pertinent information from the post-authorisation data reported to date. These AEs were either occurring more frequently in the AZD1222 group than in the control groups or, if balanced between groups, the events were considered ADRs for the meningococcal vaccines in the control groups (Section 5.5).

Table 23 Adverse Events Considered to Have Possibility of a Causal Association with AZD1222: Pooled Analysis (Dose 1 SD for Safety Analysis Set)

PT (MedDRA version 23.1)	Number (%) of Participants [a]	
	AZD1222 (N = 10317)	Control (N = 10141)
Vomiting [b, c, d]	31 (1.8)	15 (0.9)
Diarrhoea [b, c]	160 (1.6)	148 (1.5)
Pain in extremity [c]	131 (1.3)	86 (0.8)
Influenza like illness	109 (1.1)	71 (0.7)
Dizziness [b, c]	77 (0.7)	72 (0.7)

PT (MedDRA version 23.1)	Number (%) of Participants [a]	
	AZD1222 (N = 10317)	Control (N = 10141)
Abdominal pain	66 (0.6)	39 (0.4)
Somnolence [b, c]	47 (0.5)	35 (0.3)
Hyperhidrosis	42 (0.4)	20 (0.2)
Pruritus [b, c]	35 (0.3)	33 (0.3)
Lymphadenopathy [b]	29 (0.3)	28 (0.3)
Rash [b, c]	25 (0.2)	33 (0.3)
Urticaria	7 (0.1)	6 (0.1)

[a] Number (%) of participants with AEs, sorted in decreasing frequency for PT of AZD1222 group.

[b] Listed in Menveo (EU SmPC)

[c] Listed in Nimenrix (EU SmPC)

[d] Incidence for PT of Vomiting presented from Table 1.5.1.3.2 (Summary of Systemic Solicited Adverse Events)

Source: Main Safety Tables 1.5.1.3.2 and 1.5.2.2.2, Module 5.3.5.3.

5.4.2 Serious Adverse Events

In the Any Dose for Safety Analysis Set, 0.9% of participants in the AZD1222 group and 1.1% of participants in the control group reported an SAE (see Main Safety Table 1.5.3.1.1, Module 5.3.5.3). Few participants (4 subjects) reported events that were considered related to study intervention (see Main Safety Table 1.5.3.2.1, Module 5.3.5.3).

The following SAEs (PTs) were reported by the investigator as related to treatment in the AZD1222 group in the Any Dose for Safety Analysis set: pyrexia and myelitis transverse (see Main Safety Table 1.5.3.2.1, Module 5.3.5.3). Autoimmune haemolytic anaemia and myelitis were reported as related SAEs in the control group.

With the exception of a lower incidence of COVID-19 and COVID-19 pneumonia SAEs in the AZD1222 group, there were no clinically meaningful imbalances in the incidence of SAEs by SOC or PT between the AZD1222 and control groups. The most frequently reported SAEs by SOC in the AZD1222 group were Infections and infestations (0.2% [23 participants] in the AZD1222 group and 0.3% [41 participants] in the control group), Gastrointestinal disorders (0.1% [15 participants] in the AZD1222 group and 0.1% [13 participants] in the control group) and Injury, poisoning and procedural complications (0.1% [15 participants] in the AZD1222 group and 0.1% [17 participants] in the control group). The most frequently reported SAEs by PT in the AZD1222 group were appendicitis, diverticulitis, and pancreatitis; all other PTs were reported by ≤2 participants in the AZD1222 group.

Three cases of potential immune-mediated neurological (demyelinating) conditions were reported as SAEs (see Main Safety Table 1.5.3.1.1, Module 5.3.5.3); these events were also determined to be AESIs and are therefore discussed in Section 5.4.3.

A total of 7 SAEs with a fatal outcome (2 in the AZD1222 group and 5 in the control group) occurred as of the cut-off date (see Main Safety Table 1.5.3.5.1, Module 5.3.5.3). [redacted] None of these events in either the AZD1222 or control groups were considered related to study intervention by the investigator.

For narratives of related SAEs, SAEs due to COVID-19, and deaths, see Safety Narratives, Module 5.3.5.3.

5.4.3 Adverse Events of Special Interest

Pre-specified AESIs for AZD1222 included neurologic, vascular, haematologic, and immunologic events. Overall, in the Any Dose for Safety Analysis Set, the incidence of AESI was low (0.9% of participants in the AZD1222 group and 1.3% of participants in the control group). For all AESIs, there were no clinically meaningful imbalances in the incidence of AESIs by category or PT.

Neurologic Events and Potential Immune-mediated Neurologic Conditions

Within the categories of neurologic conditions and potential immune mediated neurologic conditions, the most frequently reported PTs (≥ 5 participants in the AZD1222 group) were paraesthesia (0.3% [42 participants] in the AZD1222 group vs 0.4% [51 participants] in the control group), hypoaesthesia (0.1% [15 participants] in the AZD1222 group vs 0.2% [20 participants] in the control group), and muscular weakness (0.1% [7 participants] in the AZD1222 group and 0.1% [9 participants] in the control group) (see Main Safety Table 1.5.4.1, Module 5.3.5.3). Nonserious AEs of facial paralysis occurred in 4 participants in the AZD1222 group (discussed further below) and 3 participants in the control group

Three cases of potential immune-mediated neurological demyelinating conditions were reported (see Main Safety Table 1.5.3.1.1, Module 5.3.5.3). The PTs for the 2 cases in the AZD1222 group were myelitis transverse, and multiple sclerosis; and in the control group, one case of myelitis occurred. For more detailed case descriptions see below, and for complete narratives for these events, see Safety Narratives, Module 5.3.5.3 for narratives for these events.

The event of transverse myelitis (PT: myelitis transverse) in the AZD1222 group occurred in a [redacted]-year-old female [redacted]

[redacted]

The event of multiple sclerosis in the AZD1222 group occurred in a [redacted]-year-old female [redacted]

The event of myelitis in the control group (MenACWY) occurred in a [redacted]-year-old male who [redacted].

A total of 4 cases of facial paralysis occurred in the AZD1222 group, and 3 cases occurred in the control group. Of the 4 cases in the AZD1222 group, 3 occurred in participants who received only the first dose of study vaccination; while 1 participant reported Bell's palsy approximately 51 days after the first dose of vaccination (21 days after the second dose) (data on file). Brief narrative of these 4 cases are provided below.

- A [redacted]-year-old male participant reported [redacted].
- A [redacted]-year-old female participant reported [redacted]

- A [redacted]-year-old male reported [redacted]
- A [redacted]-year-old male reported [redacted].

The 3 nonserious events of facial paralysis in the control group (MenACWY) occurred in a [redacted]-year-old female participant [redacted], a [redacted]-year-old female participant [redacted]s, and a [redacted]-year-old female participant [redacted].

One AESI of [redacted] was reported in the AZD1222 group, which was considered to be an SAE by the investigator (data on file).

- A [redacted]-year-old female reported [redacted]

Immunologic Reactions

In the [redacted].

One event of [redacted] was reported 8 days after vaccination in the [redacted] group. While not included as a pre-specified AESI, angioedema may be of clinical interest. [redacted].

Vaccine-Associated Enhanced Disease

There was no evidence of an association between AZD1222 and PTs related to COVID-19 AEs, which were reported by a numerically lower number of participants in the AZD1222 group (15 participants [0.1%]) compared with the control group (36 participants [0.3%]) (see Main Safety Table 1.5.4.1, Module 5.3.5.3). Two participants in the AZD1222 group had SAEs of COVID-19, compared with 17 participants in the control group who had serious events of COVID-19 and 4 participants had COVID-19 pneumonia (see Main Safety Table 1.5.3.1.1, Module 5.3.5.3).

For AESIs for the Dose 1 SD for Safety Analysis Set, see Main Safety Table 1.5.4.2, Module 5.3.5.3.

5.4.4 Laboratory Evaluations

A subgroup of participants had blood collected at different time points after each vaccination for clinical laboratory evaluations (3, 7, 14, or 28 days after each dose). In this subset of participants in the Any Dose for Safety Analysis Set, haematology and biochemistry laboratory results were generally similar between participants who received any dose of AZD1222 and control (see Main Safety Tables 1.6.1.1 and 1.6.2.1, Module 5.3.5.3). The proportion of participants with decreases in leukocytes, decreases in neutrophils, and decreases in thrombocytes was slightly higher in the AZD1222 group compared with control; the results for other haematology parameters were similar between the 2 groups. Few AEs related to haematology parameters and few ≥ Grade 3 haematology results were reported for both the AZD1222 and control groups (see Main Safety Table 1.5.2.2.1, Module 5.3.5.3). The clinical laboratory results in the AZD1222 group do not raise any safety concerns.

5.4.5 Safety in Subgroups

5.4.5.1 Adults with Comorbid Conditions

Over a third of participants (36.5% in the AZD1222 group and 36.7% in the control group) had a comorbidity at baseline that is considered a risk factor for COVID-19 (Main Safety Table 1.1.4.1, Module 5.3.5.3). The most common comorbid conditions in participants with comorbidity at baseline were obesity (54.5%), hypertension (25.5%), and asthma (18.8%). For details of specific comorbidities within this subgroup, see Comorbidity Safety Table 2.1.4.1.a. The demographic and baseline characteristics were consistent between comorbidity subgroups (see Comorbidity Safety Tables 2.1.3.1.a, 2.1.3.1.b, 2.1.4.1.a, and 2.1.4.1.b, Module 5.3.5.3).

AZD1222 was well tolerated in the comorbidity subgroups, with no increased reactogenicity observed in participants with comorbidities at baseline compared with those without comorbidity at baseline. The frequency and severity of solicited AEs were similar in participants with and without comorbidities at baseline (see Comorbidity Safety Tables 2.5.1.1.2.a, 2.4.1.1.2.b, 2.5.1.2.2.a, 2.5.1.2.2.b, 2.5.1.3.2.a, and 2.5.1.3.2.b, Module 5.3.5.3).

The profile of unsolicited AEs with respect to PT, frequency, and severity was generally similar regardless of comorbidity status at baseline. No deaths occurred in participants with a comorbidity at baseline. There were no clinically meaningful imbalances in the incidences of SAEs and AESIs between the AZD1222 and control group for either comorbidity subgroup (see Comorbidity Safety Tables 2.5.2.1.1.a, 2.5.2.1.1.b, 2.5.2.2.1.a, 2.5.2.2.1.b, 2.5.3.1.1.a, 2.5.3.1.1.b, 2.5.4.1.a, and 2.5.4.1.b, Module 5.3.5.3).

Overall, the safety profile of AZD1222 was similar in participants with and without comorbidities at baseline.

5.4.5.2 Older Adults

Overall, 9.4% of participants were in the ≥ 65 years of age subgroup, and 6.4% of all study participants were ≥ 70 years of age. The demographic and baseline characteristics profile was generally well balanced between the AZD1222 and control groups for each age subgroup. Among participants 18 to 64 years of age, 73.8% were White; among those 65 years old and older, 93.4% were White (see Age Safety Tables 4.1.3.1.a, 4.1.3.1.b, Module 5.3.5.3).

With respect to the reactogenicity profile of AZD1222 by age group, solicited local and systemic AEs were milder and reported less frequently in older adults (≥ 65 years) compared to younger adults (18 to 64 years). Solicited AEs were milder and reported less frequently after the second vaccination than after the first vaccination in both age groups (see Age Safety Tables 4.5.1.1.2.a, 4.5.1.1.2.b, 4.5.1.2.2.a, 4.5.1.2.2.b, 4.5.1.3.2.a, and 4.5.1.3.2.b, Module 5.3.5.3).

The incidence of unsolicited AEs reported within 28 days of any AZD1222 vaccination was also lower in the in older adults ≥ 65 years of age (29.1%) compared to younger adults 18 to 64 years of age (43.3%). A majority of unsolicited AEs was mild to moderate in severity; the incidence of unsolicited AEs with severity ≥ Grade 3 reported within 28 days after any AZD1222 vaccination was low in both the older adults (1.7%) and younger adults 18 to 64 years of age (2.2%) subgroups (see Age Safety Tables 4.5.2.1.1.a and 4.5.2.1.1.b, Module 5.3.5.3).

There were no clinically meaningful imbalances in the incidence of SAEs or AESIs between the AZD1222 and control groups in either age group. In the 18 to 64 years subgroup, SAEs were reported by 0.8% (90 participants) in the AZD1222 group and 1.0% (114 participants in the control group). In the ≥ 65 years of age group, SAEs were reported by 1.4% (18 participants) in the AZD1222 group and 1.3% (13 participants) in the control group (see Age Safety Tables 4.5.3.1.1.a, 4.5.3.1.1.b, 4.5.4.1.a, and 4.5.4.1.b, Module 5.3.5.3).

Overall, the safety profile of AZD1222 was generally similar in older adults compared with younger adults 18 to 64 years of age, with older adults reporting reduced reactogenicity.

5.4.5.3 By Country

The demographic and baseline characteristics were generally well balanced across countries, with the exception of age and race. In the UK, where mean age of the general population is higher than in Brazil and South Africa, mean age of the study participants was also numerically higher than in the other two countries. In the UK, 12.6% of participants were ≥ 65 years of age compared with 6.3% in Brazil and 0.1% in South Africa (see Country Safety Tables 3.1.3.1.a, 3.1.3.1.b, and 3.1.3.1.c, Module 5.3.5.3). In the UK and Brazil, the majority of participants were White (92.2% and 69.1%, respectively), while in South Africa 70.3% of the participants were Black.

Overall, there was no clinically meaningful imbalance in the reactogenicity profile of AZD1222 across countries;however, there were notable imbalances in the frequency and severity of any solicited AE across country (see Country Safety Tables 3.5.1.1.2.a, 3.5.1.1.2.b, 3.5.1.1.2.c, 3.5.1.2.2.a, 3.5.1.2.2.b, 3.5.1.2.2.c, 3.5.1.3.2.a, 3.5.1.3.2.b, and 3.5.1.3.2.c, Module 5.3.5.3).

In the Dose 1 SD for Safety Analysis Set, an imbalance was observed in the incidence of solicited AEs reported in the AZD1222 group, with a tendency towards higher incidences in UK (94.9%) and Brazil (92.0%), compared to those reported in South Africa (68.8%). These differences were reflected in higher incidences of local and systemic solicited AEs in the AZD1222 treatment group in UK (84.8% and 82.4%, respectively) and in Brazil (87.0% and 75.0%, respectively), as compared to those in South Africa (52.4% and 56.8%, respectively). There was a difference in the type of solicited events recorded in the patient diaries, as well as different number of days for collection of the solicited AEs in the South Africa study (Day 0 to Day 6 for South Africa vs Day 0 to Day 7 for the UK and Brazil; see Appendix B of the MAA SAP, Edition 7, Module 5.3.5.3).

Similarly, for the control group, a higher incidence of local and systemic solicited AEs were observed in UK (63.9% and 70.4%, respectively) and Brazil (60% and 65%, respectively) as compared to South Africa (22.5% and 43.5%, respectively). A higher incidence of local solicited AEs with ≥ Grade 3 severity were reported in participants in AZD1222 group in South Africa (3.9%), as compared to those in UK (0.8%) and Brazil (1.0%). The incidence of systemic solicited AEs with ≥ Grade 3 severity were comparable across these three countries (see Country Safety Tables 3.5.1.1.2.a, 3.5.1.1.2.b, 3.5.1.1.2.c, 3.5.1.2.2.a, 3.5.1.2.2.b, 3.5.1.2.2.c, 3.5.1.3.2.a, 3.5.1.3.2.b, and 3.5.1.3.2.c, Module 5.3.5.3).

Although not clinically meaningful, there was a difference in the incidence of unsolicited AEs reported in the AZD1222 group observed in Brazil (60.7%), with a tendency towards higher incidences of AEs compared with the UK (28.0%) and South Africa (27.8%). For the control group, a higher incidence of unsolicited AEs observed also observed in Brazil (43.5%)

compared with the UK (21.6%) and South Africa (26.8%) (see Country Safety Tables 3.5.2.1.1.a, 3.5.2.1.1.b, 3.5.2.1.1.c, 3.5.2.2.1.a, 3.5.2.2.1b, and 3.5.2.2.1.c, Module 5.3.5.3).

In Brazil, a lower number of participants were evaluated for solicited AEs via subject diaries (~2%) when compared to UK and South Africa (35% and 97%, respectively). This discrepancy may have resulted in reporting of typical reactogenicity AEs as unsolicited AEs in greater numbers than diary users in the UK and South Africa, who recorded these type of events as solicited AEs. The most commonly reported unsolicited events in Brazil are consistent with the common reactogenicity events collected in these studies.

There were no clinically meaningful imbalances in the incidence of SAEs or AESIs between the AZD1222 and control groups in any country (see Country Safety Tables 3.5.3.1.1.a, 3.5.3.1.1.b, 3.5.3.1.1.c, 3.5.4.1.a, 3.5.4.1.b, and 3.5.4.1.c, Module 5.3.5.3).

Overall, there were no clinically meaningful differences in the safety profile of AZD1222 across countries.

5.4.5.4 Serostatus

Overall, 95.9% of participants in the Any Dose for Safety Analysis Set were seronegative at baseline (see Main Safety Table 1.1.4.1, Module 5.3.5.3). The demographics and baseline characteristics were generally comparable for seronegative and seropositive participants with the exception of race (see Serostatus Safety Tables 5.1.3.1.a and 5.1.3.1.b, Module 5.3.5.3). For the AZD1222 group, seronegative participants were predominantly White (76.4%), while seropositive participants were White or Black (45.4% and 39.9%, respectively). Based on the limited data in participants who were seropositive (366 participants in the AZD1222 group and 387 participants in control), data interpretation should be made with caution.

There were no clinically meaningful differences in the reactogenicity profile between subgroups by serostatus at baseline (see Serostatus Safety Tables 5.5.1.1.1.a, 5.5.1.1.1.b, 5.5.1.1.2.a, 5.5.1.1.2.b, 5.5.1.2.2.a, 5.5.1.2.2.b, 5.5.1.3.2.a, 5.5.1.3.2.b, 5.5.1.4.2.a, 5.5.1.4.2.b, 5.5.1.5.2.a, 5.5.1.5.2.b, Module 5.3.5.3). The unsolicited AE profile was also generally similar between subgroups (see Serostatus Safety Tables 5.5.2.1.1.a, 5.5.2.1.1.b, 5.5.2.1.2.a, 5.5.2.1.2.b, 5.5.2.2.1.a, 5.5.2.2.1.b, 5.5.2.2.2.a, and 5.5.2.2.2.b, Module 5.3.5.3). There was no evidence of a change in severity by serostatus for unsolicited AEs in AZD1222 treatment group: among participants who were seronegative at baseline, AEs with ≥ Grade 3 severity and SAEs were reported in 2.1% and 0.9%, respectively; and among participants who were seropositive at baseline, AEs with ≥ Grade 3 severity and SAEs were reported in 1.4% and 0.3%, respectively (see Serostatus Safety Tables 5.5.2.1.1.a and 5.5.2.1.1.b, Module 5.3.5.3). There were no clinically meaningful imbalances in the incidences of SAEs and AESIs between the subgroups by serostatus at baseline (see Serostatus Safety Tables 5.5.4.2.a, 5.5.4.2.b, 5.5.3.1.1.a, 5.5.3.1.1.b, Module 5.3.5.3).

Overall, there were no clinically meaningful differences in the safety profile of AZD1222 by serostatus; the safety profile for AZD1222 in seropositive participants does not raise any specific safety concerns.

5.4.6 Effect of Paracetamol

Results on the impact of prophylactic paracetamol on vaccine-associated solicited events are available from study COV001 (Folegatti et al 2020b). In this Phase I study, in 2 of the 5 study sites, a protocol amendment allowed prophylactic administration of paracetamol prior to vaccination. The effect of prophylactic paracetamol use was assessed by evaluating the occurrence of adverse reactions in the first 2 days after vaccination.

A total of 56 participants in the AZD1222 group and 57 in the control group received prophylactic paracetamol Table 24. The incidences of local and systemic solicited AEs were numerically lower among participants in the AZD1222 and control group that received prophylactic paracetamol compared with participants who did not receive prophylactic paracetamol. Adjusted analysis of the effect of prophylactic paracetamol on adverse reactions of any severity in the first 2 days after vaccination with AZD1222 showed significant reductions in injection site pain, feeling feverish, chills, muscle ache, headache, and malaise (Folegatti et al 2020b). Based on the results from this dataset, reactogenicity events were reduced by the use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise.

Table 24 Incidence of Solicited Adverse Events in the 2 Days after Vaccination in Participants with and without Prophylactic Paracetamol (COV001)

	Number (%) of Participants			
	AZD1222		MenACWY Control	
	No Paracetamol N=487	Paracetamol N=56	No Paracetamol N=477	Paracetamol N=57
Solicited Local Adverse Events				
Pain	302 (62.0)	24 (42.9)	148 (31.0)	12 (21.1)
Tenderness	382 (78.4)	42 (75.0)	243 (50.9)	20 (35.1)
Redness	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Warmth	83 (17.0)	8 (14.3)	53 (11.1)	6 (10.5)
Itch	7 (1.4)	1 (1.8)	7 (1.5)	1 (1.8)
Swelling	9 (1.8)	0 (0.0)	7 (1.5)	2 (3.5)
Induration	7 (1.4)	0 (0.0)	3 (0.6)	2 (3.5)
Solicited Systemic Adverse Events				
Fever	84 (17.2)	9 (16.1)	2 (0.4)	0 (0.0)

	Number (%) of Participants			
	AZD1222		MenACWY Control	
	No Paracetamol N=487	Paracetamol N=56	No Paracetamol N=477	Paracetamol N=57
Feverishness	24 (50.1)	19 (33.9)	22 (4.6)	5 (8.8)
Chills	265 (54.4)	15 (26.8)	30 (6.3)	3 (5.3)
Joint Pain	142 (29.2)	14 (25.0)	24 (5.0)	2 (3.5)
Muscle Pain	283 (58.1)	24 (42.9)	74 (15.5)	10 (17.5)
Fatigue	310 (63.7)	33 (58.9)	157 (32.9)	15 (26.3)
Headache	312 (64.1)	27 (48.2)	116 (24.3)	11 (19.3)
Malaise	285 (58.5)	22 (44.6)	45 (9.4)	3 (5.3)
Nausea	111 (22.8)	14 (25.0)	27 (5.7)	5 (8.8)

Source: Folegatti et al 2020b.

Analysis of potential prophylactic paracetamol use in Studies COV002 and COV003

Participants in Studies COV002 and COV003 were recommended to take prophylactic paracetamol and to self-report the use in diaries. In this dataset, there was a trend for numerically greater solicited AE incidences reported in the paracetamol use group than in the no paracetamol group among participants in the AZD1222 treatment group (see Table IEMT10.2.1.2, Module 5.3.5.3 of the original application).

Further review of the systemic solicited AEs demonstrates that this difference is generally consistent across all AEs reported in both the AZD1222 paracetamol group and AZD1222 no paracetamol group (see Table IEMT 10.2.3.2, Module 5.3.5.3 of the original application).

Understanding paracetamol use in Studies COV002 and COV003 may be confounded by compliance whereby paracetamol was not consistently taken prophylactically despite solicited AE diary data entry suggesting so. The higher rates of solicited reactogenicity in those receiving paracetamol prophylaxis suggests that paracetamol was taken in response to symptoms and that true prophylactic use may have been less than expected.

5.4.7 Use in Pregnancy and Lactation

Women who were pregnant, lactating, or intending on becoming pregnant were excluded from the University of Oxford studies, and women of childbearing capacity were required to use continuous effective birth control in all 4 studies.

As of 07 December 2020, a total of 40 pregnancies were reported in the AZD1222 pooled analysis dataset, with 24 participants in the AZD1222 group and 16 participants in the control group (see Listing IEMT 221.1, Module 5.3.5.3). In the AZD1222 group, 4 terminations of pregnancy and 4 spontaneous miscarriages were reported. In the control group, there were 3 reports of termination of pregnancy and 3 of spontaneous miscarriage. A review of the pregnancy exposure reports did not raise any safety concerns.

All pregnancies will be followed up until the pregnancy outcome is determined. Overall, there is a limited amount of data to draw any meaningful conclusions from the use of AZD1222 in pregnant women, women who became pregnant after receiving the vaccine, or lactating women.

5.5 Post-marketing Safety Reports

The Summary Safety Report for the COVID-19 VACCINE ASTRAZENECA (AZD1222) summarises safety data received and evaluated by AstraZeneca from 01 January 2021 to 31 January 2021. AstraZeneca is working directly with health departments in individual countries to determine the number of doses administered. During the reporting period, the number of doses administered in the United Kingdom was confirmed as being 3,708,571. The number of doses distributed globally is 44,496,140.

Anaphylaxis and Angioedema were included as adverse reactions from post market data based on the safety signal of serious hypersensitivity/anaphylactic reaction. Furthermore, the following adverse reactions were commonly reported based on spontaneous sources (Table 25). Please also refer to Section 5.4.1.

Table 25 Post-Market Adverse Events

PT (MedDRA version 23.1)	Total cases [a]
Dizziness	2273
Pain in extremity	1603
Vomiting	1569
Influenza like illness	1160
Hyperhidrosis	1122
Diarrhoea	974
Abdominal pain	451
Rash	442
Pruritus	436
Lymphadenopathy	306
Somnolence	190

PT (MedDRA version 23.1)	Total cases [a]
Urticaria	160

[a] Includes cases that were closed or processed in safety database until data cut-off of 15 February 2021

5.6 Safety Conclusions: Safety Profile of AZD1222

This primary pooled analysis was conducted with 24244 participants in the Any Dose for Safety Analysis, including 12282 who received at least 1 dose of AZD1222, and 11962 who received at least 1 dose of control.

Overall, vaccination with AZD1222 was well tolerated. Most solicited local and systemic AEs were mild to moderate in severity and tended to be milder and reported less frequently after the second dose than after the first dose. The most common solicited AEs, also determined to be adverse drug reactions, were fatigue, headache, malaise, feverishness, chills, joint pain, nausea, and fever and local injection site reactions (tenderness, pain, warmth, redness, itch, swelling). Unsolicited AEs were consistent with AEs commonly observed following vaccination. The unsolicited events which the Applicant considers as ADRs are: Dizziness, Somnolence, Vomiting, Diarrhoea, Abdominal Pain, Lymphadenopathy, Influenza like illness, Hyperhidrosis, Pain in extremity, Urticaria, Rash, Pruritus. Anaphylaxis and Angioedema are considered as ADRs based on post-market data.

The incidence of SAEs was low in both the AZD1222 (0.9%) and control groups (1.1%), and, with the exception of a lower incidence of COVID-19 and COVID-19 pneumonia, SAEs in the AZD1222 group, there were no clinically meaningful imbalances in the incidence of SAEs by SOC or PT between the AZD1222 and control groups., with no difference in either frequency or type of SAEs between the treatment groups. A total of 7 SAEs with a fatal outcome (2 in the AZD1222 group and 5 in the control group) occurred as of DCO2. None of these events were considered related to study intervention by the investigator.

Few AESIs were reported (0.9% of participants in the AZD1222 group and 1.3% of participants in the control group). There were no clinically meaningful imbalances in the incidence of AESIs by category or PT to suggest any association with AZD1222. Within the categories of neurologic conditions and potential immune-mediated neurologic conditions, the most frequently reported PTs were paresthesia, hypoaesthesia, and muscular weakness. The incidence of paraesthesia and hypoaesthesia was numerically lower in the AZD1222 group than in the control group, while the incidence of muscular weakness was similar between the 2 groups. Nonserious AEs of facial paralysis occurred in 4 participants in the AZD1222 group and 3 participants in the control group. [redacted]

[redacted]

There were no clinically relevant differences in the safety profile by comorbidity, or serostatus subgroup. The safety profile of AZD1222 was generally similar in older adults compared with younger adults aged 18 to 64 years of age; however, with older adults reporting milder and less frequent solicited reactogenic AEs compared with younger adults.

6 BENEFITS AND RISKS CONCLUSIONS

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The vaccine is administered IM as two 0.5 mL doses of 5×10^{10} vp (nominal), at an interval of 4 to 12 weeks. The benefits and risks of AZD1222 for this indication with the recommended vaccination regimen are described below.

6.1 Benefits of AZD1222

The updated evaluation of the efficacy of AZD1222 for prevention of COVID-19 is based on the pooled data from 4 ongoing clinical studies as of DCO2, comprising adults aged from [redacted] up to [redacted] years. 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 AZD1222 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 AZD1222 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). 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.

Further, AZD1222 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 AZD1222 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, AZD1222 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 AZD1222 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 AZD1222 use to protect against COVID-19 disease.

Finally, AZD1222 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.

6.2 Risks of AZD1222

The updated evaluation of the safety of AZD1222 is based on the pooled population from 4 ongoing studies, comprising 24244 male and female adults aged from [redacted] years to [redacted] years, who received at least one dose of study drug (12282 received AZD1222 and 12282 received control) up to the DCO2date. A majority (85.1%) of participants in the AZD1222 group had received 2 standard doses, which is the recommended dosing regimen. The median exposure time was similar in the AZD1222 (119 days) and the control groups (118 days) in the Dose 1 SD Safety analysis set, and following the second dose (74 days for both groups).

Overall, vaccination with AZD1222 was well tolerated. The incidence of SAEs was low in both the AZD1222 (0.9%) and control (1.1%) groups, with no difference in either frequency or type of SAEs between the treatment groups. There were 7 SAEs with a fatal outcome (2 in the AZD1222 group and 5 in the control group), but none of these was considered treatment related by the investigator. The majority of AEs were mild to moderate in severity, and they were generally milder and reported less frequently after the second dose than after the first dose. The most common AEs, also determined as adverse drug reactions, were fatigue, headache, muscle pain, malaise, feverishness, chills, joint pain, nausea, and fever and local injection site reactions (tenderness, pain, warmth, redness, itch, swelling). These are either common class effects of vaccines or commonly observed injection site reactions following IM injections, and were generally mild to moderate and self-limiting. Apart from the above most common AEs (based on a detailed assessment by an AstraZeneca internal peer review panel of data), the Applicant considers the following AEs as ADRs : Dizziness, Somnolence,

Vomiting, Diarrhoea, Abdominal Pain, Lymphadenopathy, Influenza like illness, Hyperhidrosis, Pain in extremity, Urticaria, Rash, Pruritus.

The most frequently reported neurologic AESIs were paraesthesia, hypoaesthesia and muscular weakness, with a numerically lower incidence in the AZD1222 group than in the control group. For neurological events overall, there were no imbalances raising safety concerns between the AZD1222 and control groups.

Further, no imbalances raising safety concerns were observed between the AZD1222 and control group for any potential immune-mediated conditions. There were 3 SAEs of demyelinating events; [redacted] Based on the available safety data, there is no evidence suggesting a causal relationship between AZD1222 and these singular events of demyelinating disorders. However, since vaccinations could be associated with immune-mediated neurological conditions, these are included as an important potential risk in the RMP.

There is a theoretical concern that vaccination could be associated with VAED, therefore it is included as an important potential risk in the RMP. However, AESIs related to COVID-19 were reported at numerically lower frequency in the AZD1222 group (0.1%) than in the control group (0.3%), and therefore, the data do not suggest an association between AZD1222 and VAED.

Regarding sub-populations, there were no clinically meaningful differences in the safety findings between subgroups with and without comorbidities, or between subgroups of younger (18-64 years) and older (≥ 65 years) adults.

One limitation in the current safety evaluation of AZD1222 is the limited duration of follow-up. Long-term follow-up of the ongoing clinical studies (up to 1 year) will provide data to further characterise the safety profile of AZD1222. Moreover, since people with severe immunodeficiencies, severe underlying comorbid disease, and pregnant/lactating women were excluded from the studies, the safety of AZD1222 in these groups is currently unknown.

6.3 Benefit Risk Assessment

Updated data from the primary efficacy analysis confirmed protection by AZD1222 against symptomatic COVID-19, as originally shown by the interim analysis. Additionally, we have provided robust evidence that AZD1222 confers complete protection against severe cases of COVID-19, as well as 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 AZD1222 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 preexisting disease are at higher risk of severe COVID-19 outcomes and have the greatest unmet medical need among the general population. The updated results presented in this submission still show consistent vaccine efficacy against COVID-19, both in participants with or without background comorbidities. Regarding protection in older adults (≥ 65 years), events experienced in this population were still too few to draw significant conclusions about vaccine efficacy, but trends shown in the updated data were in line with those in the general population. Moreover, the humoral antibody response in older adults tended to be more similar to those of adults [redacted] years of age when dose interval was taken into account. The safety profiles in those with comorbidities as well as the older adults were generally similar to that in the overall population. Thus, the benefit-risk profile is considered similar in the subgroups with comorbidities and/or older age, as in the general adult population.

There are no important identified risks with AZD1222 vaccination. Very rare events of demyelinating disorders were reported both in the AZD1222 and control groups, however, there is no evidence suggesting a causal relationship between AZD1222 and demyelinating disorders. Nevertheless, immune-mediated neurological conditions are included as an important potential risk in the RMP, due to a theoretical concern of association with vaccines. The association between vaccines and acute demyelinating events has been assessed in a range of studies and expert reviews. A population-based analysis of nearly 64 million vaccine doses in the US, concluded that if there is any association between transverse myelitis and vaccines, it is < 2 per million doses of live zoster and live attenuated influenza vaccines, and < 1 per million doses for other vaccines (Baxter et al 2016). Regarding multiple sclerosis, most studies suggest no causative effect for onset, but possibly for flares or relapses (Mailand and Frederiksen 2017). Moreover, demyelinating diseases occur more frequently with infections than with vaccination (McMahan et al 2020; Miravalle et al 2010). Taken together, the evidence is inconclusive regarding a causal relation between contemporary vaccines and acute demyelinating events (Mouchet et al 2018; Phillips et al 2018; Principi and Esposito 2020). Overall, the benefits of AZD1222 vaccination both for the individual and for public health are considered to outweigh the potential risk of immune-mediated neurological events. However, a precautionary note to prescribers to consider the benefits and potential risks of AZD1222 vaccination in individuals is included in the Core Data Sheet. Regarding VAED, there is a theoretical risk in relation to AZD1222 vaccination, however, as there were no data suggesting an association between AZD1222 and VAED, no impact on public health is anticipated.

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, AZD1222 is considered appropriate to address this urgent unmet medical need. Moreover, the easy storage and handling of the AZD1222 formulation is expected to be an important additional benefit that enables wide access to the vaccine.

In conclusion, the benefit-risk profile of AZD1222 has been shown to be consistently favourable, over two data cut-offs, 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. Moreover, this updated submission provided additional data in support of the approved indication for AZD1222. Thus, AZD1222 is anticipated to have a significant impact both for individuals and on public health in the ongoing COVID-19 pandemic.

7 REFERENCES

Antrobus et al 2014
Antrobus RD, Coughlan L, Berthoud TK, Dicks MD, Hill AV, Lambe T et al. Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. Molecular therapy : the journal of the American Society of Gene Therapy. 2014;22(3):668-74.

Arentz et al 2020
Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020;323(16):1612-4.

Atyeo et al 2020
Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C et al. Distinct early serological signatures track with SARS-CoV-2 survival. Immunity. 2020;53(3):524-32.e4.

Ayres 2020
Ayres JS. A metabolic handbook for the COVID-19 pandemic. Nat Metab. 2020; 2: 572-585.

Baden et al 2020
Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, .et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384:403-416.

Barouch et al 2018
Barouch DH, Tomaka FL, Wegmann F, Stieh DJ, Alter G, Robb ML et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet (London, England). 2018;392(10143):232-43.

Barrett et al 2020
Barrett JR, Belij-Rammerstorfer S, Dold C, Ewer KJ, Folegatti PM, Gilbride C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. 2020 Dec 17. (IN PRESS)

Baxter et al 2016
Baxter R, Lewis E, Goddard K, Fireman B, Bakshi N, DeStefano F, et al. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clin Inf Dis. 2016; 63 (11): 1456–62. https://doi.org/10.1093/cid/ciw607

Billeskov et al 2017
Billeskov R, Wang Y, Solaymani-Mohammadi S, Frey B, Kulkarni S, Andersen P, et al. Low Antigen Dose in Adjuvant-Based Vaccination Selectively Induces CD4 T Cells with Enhanced Functional Avidity and Protective Efficacy. J Immunol. 2017 May 1;198(9):3494-3506.

Cappuccini et al 2020
Cappuccini F, Bryant R, Pollock E, Carter L, et al (2020), Safety and immunogenicity of novel 5T4 viral vectored vaccination regimens in early stage prostate cancer: a phase I clinical trial. J Immunother Cancer. 2020 Jun;8(1):e000928

Centers for Disease Control and Prevention, 2020
Centers for Disease Control and Prevention. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020 69: 343-346.

Coughlan et al 2018
Coughlan L, Sridhar S, Payne R, Edmans M, Milicic A, Venkatraman N et al. Heterologous Two-Dose Vaccination with Simian Adenovirus and Poxvirus Vectors Elicits Long-Lasting Cellular Immunity to Influenza Virus A in Healthy Adults. EBioMedicine. 2018 Mar;29:146-154. doi: 10.1016/j.ebiom.2018.02.011. Epub 2018 Feb 15. Erratum in: EBioMedicine. 2018 May 4.

Dicks et al 2012
Dicks MD, Spencer AJ, Edwards NJ, Wadell G, Bojang K, Gilbert SC et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PloS one. 2012;7(7):e40385.

Dudareva et al 2009
Dudareva M, Andrews L, Gilbert SC, Bejon P, Marsh K, Mwacharo J et al. Prevalence of serum neutralizing antibodies against chimpanzee adenovirus 63 and human adenovirus 5 in Kenyan children, in the context of vaccine vector efficacy. Vaccine. 2009;27(27):3501-4.

Ewer et al 2020
Ewer, K.J., Barrett, J.R., Belij-Rammerstorfer, S. et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med (2020).

Emary et al 2021
Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus BJ, Bibi S, et al. 2021. Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 VOC 202012/01 (B.1.1.7). Lancet. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

Folegatti et al 2019
Folegatti PM, Harrison K, Lopez FR, Tilley MW, Lopez-Camacho C, Kim YC et al. Safety and immunogenicity of a replication deficient simian adenoviral vectored chikungunya vaccine: A phase I, first-in-human, dose escalation trial. Abstract 59. American Society of Tropical Medicine and Hygiene Annual Meeting. 2019;101(5 [Supplement]):19.

Folegatti et al 2020a
Folegatti PM, Bittaye M, Flaxman A, Lopez FR, Bellamy D, Kupke A et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. Lancet Infect Dis. 2020 Jul;20(7):816-826. doi: 10.1016/S1473-3099(20)30160-2. Epub 2020 Apr 21. Erratum in: Lancet Infect Dis. 2020 May 12; Erratum in: Lancet Infect Dis. 2020 Jun 8.

Folegatti et al 2020b
Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug 15;396(10249):467-78. Epub 2020 Jul 20. Erratum in: Lancet. 2020 Aug 15;396(10249):466.

Grasselli et al 2020
Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020.

Guan et al 2020
Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

Guzik et al 2020
Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666-87.

Hassan et al 2020
Hassan AO, Kafai NM, Dmitriev IP, Fox JM, Smith BK, Harvey IB et al. A Single-Dose Intranasal ChAd Vaccine Protects Upper and Lower Respiratory Tracts against SARS-CoV-2. Cell. 2020 Oct 1;183(1):169-84.e13.

Lee et al, 2017
Lee CS, Bishop ES, Zhang R, Yu X et al. Adenovirus-mediated gene delivery: Potential applications for gene and cell-based therapies in the new era of personalized medicine. Genes & Disease. 2017; 4: 43-63.

Li et al 2017
Li JX, Hou LH, Meng FY, Wu SP, Hu YM, Liang Q et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Glob Health. 2017 Mar;5(3):e324-e334. doi: 10.1016/S2214-109X(16)30367-9. Epub 2016 Dec 23. PMID: 28017642.

Liu et al 2020
Liu Y, Wang K, Massoud T, Ramasamy Paulmurugan R. SARS-CoV-2 Vaccine Development: An Overview and Perspectives. ACS Pharmacology & Translational Science. 2020; 3 (5), 844-858. doi: 10.1021/acsptsci.0c00109.

Madhi et al 2021
Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AK, Fairlie L, et al. 2021. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. Medrxiv (the preprint server for Health Sciences, Cold Spring Harbor Laboratory). https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1

Madjid et al 2020
Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;5(7):831-40.

Mailand and Frederiksen 2017
Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. J Neurol. 2017;264(6):1035-50.

Marshall et al 2020
Marshall JC, Murthy S, Diaz J, Adhikari N, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-10 clinical research. Lancet Inf Dis 2020 20:8 (e192-e197).

McMahan et al 2020
McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature. 2020 Dec 4.

Miravalle et al 2010
Miravalle A, Biller J, Schnitzler E, Bonwit A. Neurological complications following vaccinations. Neurol Res. 2010;32(3):285-92.

Morris et al, 2017
Morris SJ, Sebastian S, Spencer A, Gilbert SC. Simian adenoviruses as vaccine vectors. Future Virol. 2016; 11(9): 649–659.

Moscola et al 2020
Moscola J, Sembajwe G, Jarrett M, et al. Prevalence of SARS-CoV-2 Antibodies in Health Care Personnel in the New York City Area. JAMA. 2020; 324(9):893–895.

Mouchet et al 2018
Mouchet J, Salvo, F, Raschi E, Poluzzi E, Antonazzo IC, De Ponti F, et al. Hepatitis B vaccination and the putative risk of central demyelinating diseases – a systematic review and meta-analysis. Vaccine. 2018;36: 1548–55.

Polack et al 2020
Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15

Phillips et al 2018
Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of Human Papillomavirus Vaccines: An Updated Review. Drug Saf. 2018;41:329–46.

Principi and Esposito 2020
Principi N and Esposito S. Do Vaccines have a role as a cause of autoimmune neurological syndromes? Front Public Health 2020;8:361. doi: 10.3389/fpubh.2020.00361

Tatsis et al 2007
Tatsis N, Blejer A, Lasaro MO, Hensley SE, Cun A, Tesema L et al. A CD46-binding chimpanzee adenovirus vector as a vaccine carrier. Molecular therapy: The Journal of the American Society of Gene Therapy. 2007;15(3):608-17.

Tuthill et al 2020
Tuthill M, Cappuccini M, Carter L, Pollock E et al. Results from ADVANCE, a Phase I/II open-label non-randomised safety and efficacy study of the viral vectored ChAdOx1-MVA 5T4 (VTP-800) vaccine in combination with PD-1 checkpoint blockade in metastatic prostate cancer. Ann Oncol 2020; 31:S543

Ramasamy et al 2020
Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost

regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020 Nov 18:S0140-6736(20)32466-1.

Shi et al 2020
Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10.

Voysey et al 2020
Voysey M, Clemens SAC, Madhi SA, Weckx, LY, Folegatti PM, Aley PK et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. Epub 2020 Dec 20. doi.org/10.1016/S0140-6736(20)32661-1.

WHO 2020a
WHO. (World Health Organization) WHO Corona Virus Disease (COVID 19) Dashboard. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 14 December 2020.

Wilkie et al 2020
Wilkie M, Satti I, Minhinnick A, Harris S, et al . A phase I trial evaluating the safety and immunogenicity of a candidate tuberculosis vaccination regimen, ChAdOx1 85A prime - MVA85A boost in healthy UK adults. Vaccine.2020 Jan 22;38(4):779-789

Williamson et al
Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430-36.

Zabdeno EPAR 2020
Zabdeno European public assessment report: EMA/323670/2020. 28 May 2020. Available from: https://www.ema.europa.eu/en/documents/assessment-report/zabdeno-epar-public-assessment-report_en.pdf. Accessed 10 December 2020.

Zhou et al 2020
Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.

Zhu et al 2020
Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020 Aug 15;396(10249):479-88.

8 LIST OF APPENDICES

8.1 Appendix A – Low Dose Delivery of AZD1222 in Study COV002 and Study COV005