2.5 Clinical Overview	
Drug Substance	AZD1222
Date	21 December 2020

2.5 Clinical Overview

AZD1222 Marketing Authorisation Application

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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).
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
ICS	intracellular cytokine staining
IFNγ	interferon gamma

Abbreviation or special term	Explanation
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
UK	United Kingdom
VAED	vaccine-associated enhanced disease

Abbreviation or special term	Explanation
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 data cut-off date for the interim pooled analyses included in this application was 04 November 2020.

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacological Class

COVID-19 Vaccine AstraZeneca (AZD1222) 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 Proposed Indication and Dosing

The Applicant seeks conditional marketing authorisation of COVID-19 Vaccine AstraZeneca (AZD1222) for active immunisation of individuals ≥ 18 years old, for the prevention of coronavirus disease 2019 (COVID-19). The vaccine will be 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 2020b). 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.

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 Applicant is seeking Conditional Marketing Authorization for COVID-19 Vaccine AstraZeneca (AZD1222) 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 roles of S in receptor binding and membrane fusion make it a desirable 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 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.

In the present conditions of an extreme public health emergency, and in consultation with MHRA, EMA, and other regulatory authorities, the Applicant has developed a strategy to produce early and robust estimates of the efficacy, safety, and immunogenicity of AZD1222 based on a pooled analysis of ongoing studies.

Data is 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 protocol version 12.0, COV002 protocol version 14.0, COV003 protocol version 8.0, COV005 protocol 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	II/III	I/II
Design	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Double blind, randomised, controlled
Planned number of participants	~ 1077	~12390	~10300	~2070
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
Planned Dose interval	4 – 8 wk	4 – 6 wk	4- 12 wk	4 wk
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

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**
Case detection	Passive	Passive and active (weekly contacts)	Not applicable	Passive	Passive
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

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

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

[e] 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 4 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

Topic(s)	Agency Advice
Scientific advice: 04 September 2020 (MHRA; 2369/AZD1222 COVID-19 vaccine); 11 September 2020 (EMA; EMEA/H/SA/4655/1/2020/II)	
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 expected mid-December 2020

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).

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

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 reference 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. 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). 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).

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 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 4.2.9.3).

3.4 Cell-mediated Immunity

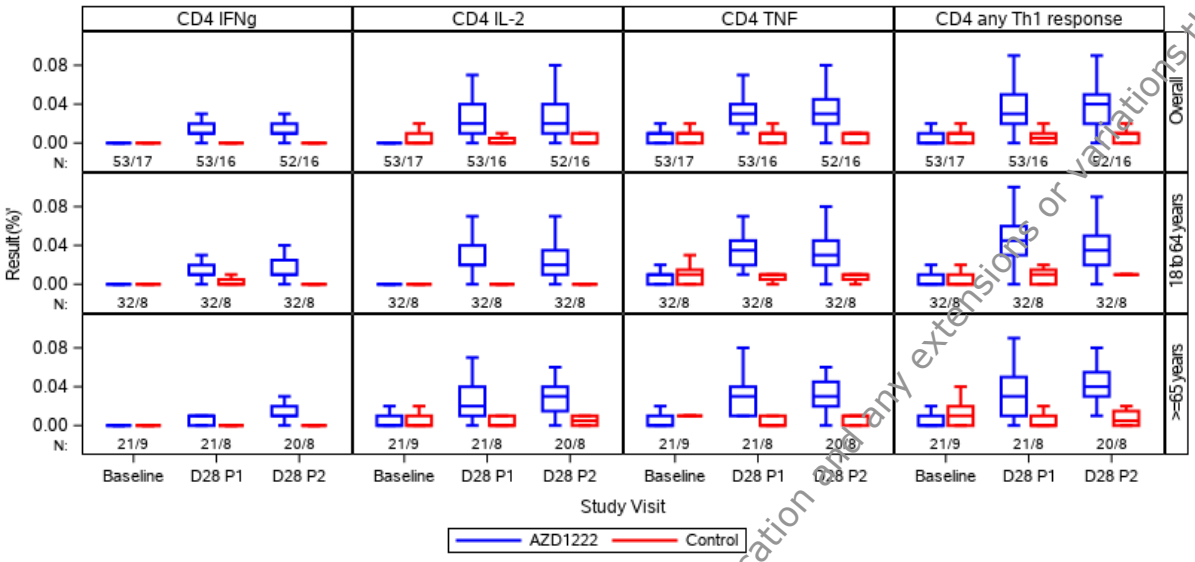
Assessment of cell-mediated immunity is important for the assessment of safety (ie, Th1/Th2 polarization) as well as the potential vaccine efficacy (McMahan et al 2020). Cell-mediated immunity was assessed by two different methods in the Immunogenicity Analysis Set of the pooled analysis: IFNγ ELISpot 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 (04 November 2020); all data represent the UK subgroup.

S-specific T cell responses as analysed by IFNγ+ ELISpot suggest that T cells are induced after a first dose of AZD1222 (with geometric means responses of 584.384, 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 (see Immuno Table 1.7.3.1.1; Li et al 2017). Indeed, IFNγ+ SFCs peaked around Day 14 when responses were analysed at Day 7, Day 14, and Day 28 post first dose, indicating the potential for T cell-mediated responses to contribute to protection from disease after a first dose of AZD1222 (see Immuno Figure 1.7.4.1.1). ELISpot data similarly suggest that IFNγ+ T cell responses were comparable in subgroups, with age (18 to 64 years: GMR = 681.335, ≥ 65 years: GMR = 518.621; see Immuno Tables 4.7.3.1.1.a and 4.7.3.1.1.b) and comorbidity (comorbidity: GMR = 630.589, no comorbidity: GMR = 550.890, see Immuno Tables 2.7.3.1.1.a and 2.7.3.1.1.b) after a first dose, which were not further increased after a second dose.

ICS was performed on 70 participants (40, 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-12, 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 IEMT60.1 and IEMT60.2). 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 IEMT60.1.1.1.
Additional figure for Th1 cytokine expression in SARS-CoV-2 S2 stimulated PBMCs presented in Supplemental Figure IEMT60.1.1.2.

4 OVERVIEW OF EFFICACY

4.1 Introduction

The pooled analysis provided in this application includes interim 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 pre-specified criteria for breaking the blind for the study and triggering the interim pooled analysis was based on overwhelming evidence of efficacy and was recommended by the independent DSMB. Evidence of efficacy for AZD1222 is based on pooled data from Studies COV002 and COV003; these studies are included in the pooled interim analysis for efficacy based on having met the predetermined criterion of at least 5 cases of COVID-19. Evidence of immunogenicity and safety for AZD1222 is based on pooled data from all 4 studies. The Health Authorities have endorsed the strategy for this pooled interim 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 inclusion and exclusion criteria were generally similar across studies. All studies enrolled adults 18 to 55 years of age. In addition, Studies COV002 and COV003 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 underlying health conditions with the exception of severe and/or uncontrolled underlying disease. All studies excluded pregnant and breastfeeding women.

Subgroups that would make interpretation challenging were prespecified per SAP and excluded from the pooled analysis data set. These included subgroups that were not randomized and therefore there was 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 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 interim analyses.

Case definitions for the pooled analysis are presented in Table 5. Per protocol, in UK studies, ICU admission was a protocol-defined endpoint. In order to standardise "ICU admission" across studies for differences in local medical practice, this was redefined as "Requiring ICU admission" and corresponds to those cases with WHO severity grades reflecting the need for mechanical ventilation.

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. Confirmed by adjudication committee.
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]

Case	Definition
Asymptomatic SARS-CoV-2 infection	Virologically confirmed SARS-CoV-2 infection and no symptom record in data. Confirmed by adjudication committee.
Asymptomatic and unknown symptoms SARS-CoV-2 infection	Virologically confirmed SARS-CoV-2 infection and no symptom record in data or symptoms unknown. 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 6, M 5.3.5.3).

This interim pooled analysis was planned to be triggered when at least 53 cases of SARS-CoV-2 virologically confirmed symptomatic COVID-19 that occurred ≥ 15 days post the second dose had been reported in participants who received SDSD across the AZD1222 and control groups in pooled studies. This was expected to provide approximately 80% power for the 20% threshold for an assumed vaccine efficacy of 70% for the primary population (participants who received SDSD and LDSD). The Health Authorities have endorsed the testing strategy for this pooled interim analysis (Section 1.5.1). Due to the rapid accumulation of cases prior to database cut-off, 131 events were included in the analysis, of which 98 were in participants that received the SDSD regimen.

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).

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 6, 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. 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 are testing hypotheses against a vaccine efficacy of 0%. For the primary endpoint efficacy objective to be met, the lower bound of the CI for the vaccine efficacy must be > 20%. A 95.84% CI is used for the primary endpoint in the SDSD + LDSD Seronegative for Efficacy Analysis Set, as well as the corresponding SDSD + LDSD seronegative ITT, SDSD seronegative, and LDSD seronegative efficacy analysis populations (Table 8). All remaining efficacy analyses used a 95% CI.

For analyses of endpoints where there were rare events, 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.

For a complete description of the statistical methods, see Sections 9 (Efficacy) and 11 (Immunogenicity) of the SAP (see MAA SAP, Edition 6, 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 and are described in this document:

- Age at screening;
  - 18 to 64 years, ≥ 65 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. The analysis of the LDSD was pre-defined as an exploratory subgroup analysis. For ease of review, all tables show the primary cohort for analysis of SDSD + LDSD alongside the SDSD and LDSD cohorts. 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					12018	11735	23753
Safety							
Any Dose for Safety [a]	As treatment received	Pos and Neg and Missing	Any	From Dose 1	12021	11724	23745
Dose1 SD for Safety [a]	As treatment received	Pos and Neg and Missing	SDSD SD single dose SDLD	From Dose 1	10069	9902	19971
Efficacy							
Any Dose for Efficacy [a]	As treatment received	Pos and Neg and Missing	Any	From Dose 1	10014	10000	20014
SDSD + LDSD Seronegative for Efficacy [b] (Primary population)	As treatment received	Seronegative	SDSD LDSD	From 15 days post Dose 2	5807	5829	11636
SDSD + LDSD Seronegative ITT for Efficacy [b]	As randomized	Seronegative	SDSD LDSD	From 15 days post Dose 2	5814	5831	11645
SDSD Seronegative for Efficacy [b]	As treatment received	Seronegative	SDSD	From 15 days post Dose 2	4440	4455	8895
LDSD Seronegative for Efficacy [b]	As treatment received	Seronegative	LDSD	From 15 days post Dose 2	1367	1374	2741
Dose1 SD Seronegative for efficacy [c]	As treatment received	Seronegative	SDSD SD single dose SDLD	From 22 days post Dose 1	6307	6297	12604

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 [c]	As treatment received	Seronegative	LDSD LD single dose LDLD	From 22 days post Dose 1	1687	1686	3373
Immunogenicity							
SDSD + LDSD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SDSD LDSD	All available timepoints	1666	1205	2871
SDSD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SDSD	All available timepoints	1367	1031	2398
LDSD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	LDSD	All available timepoints	299	174	473

[a] Analyses on these sets use data starting from first dose.

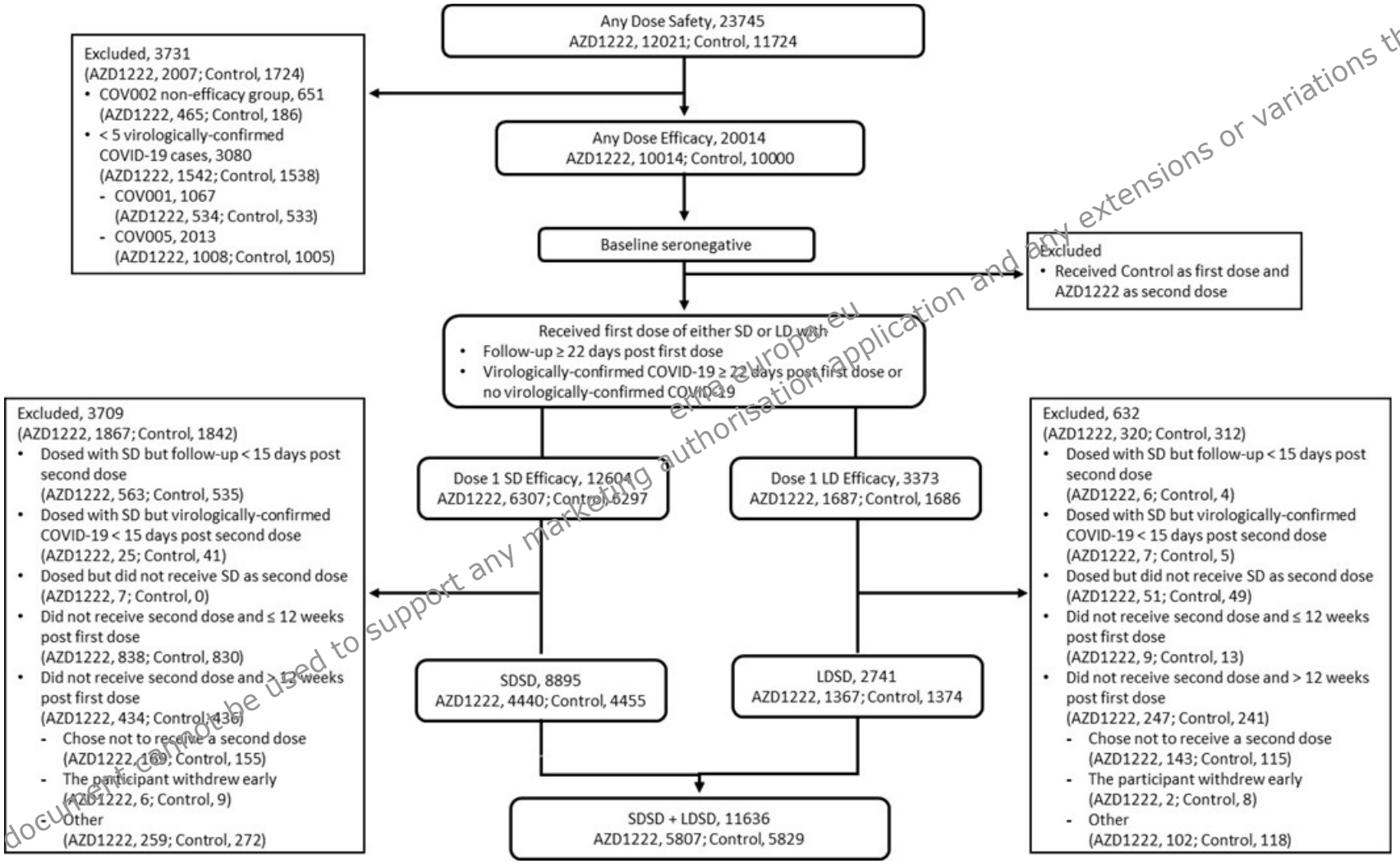
[b] Analyses on these sets use data starting from ≥ 15 days post the second dose.

[c] Analyses on these sets use data starting from ≥ 22 days post the first dose.

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

Source: Main Safety Tables 1.1.1.1 and 1.1.1.2; Immuno Table 1.1.1.2

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; Supplemental Tables IEMT55.1 and IEMT55.2.

4.2.1.2 Exposure to AZD1222

As of the data cut-off date of 04 November 2020, 12021 participants of the 4 studies included in the application have received at least one dose of AZD1222. Of these participants, 8266 (68.8%) have received 2 doses of AZD1222 (Table 7; see Main Safety Table 1.2.1.1).

Overall and in the primary efficacy analysis set, approximately one-third of participants each had a dose interval in the range of < 6 weeks, 6 to 11 weeks, or ≥ 12 weeks. The distribution of participants across the range of dose intervals is discussed by dosing regimen and by country in Section 4.2.8 and presented in Table 19.

Table 7 Exposure to Study Intervention at the time of data cut-off

Parameter		Any Dose for Safety Analysis Set		SDSD + LDSD Seronegative for Efficacy Analysis Set	
		AZD1222 (N = 12021)	**Control (N = 11724)**	**AZD1222 (N = 5807)**	**Control (N = 5829)**
Dose level [a], n (%)	LDSD	1516 (12.6)	1472 (12.6)	1367 (23.5)	1374 (23.6)
	LDLD	127 (1.1)	69 (0.6)	0	0
	SDSD	6568 (54.6)	6472 (55.2)	4440 (76.5)	4455 (76.4)
	SDLD	55 (0.5)	36 (0.3)	0	0
	LD	305 (2.5)	281 (2.4)	0	0
	SD	3450 (28.7)	3394 (28.9)	0	0
	Total	12021	11724	5807	5829
Dose interval, n(%)	< 6 weeks	3412 (41.3)	3234 (40.2)	1702 (29.3)	1698 (29.1)
	6-8 weeks	680 (8.2)	604 (7.5)	568 (9.8)	527 (9.0)
	9-11 weeks	1558 (18.8)	1550 (19.3)	1444 (24.9)	1488 (25.5)
	≥ 12 weeks	2616 (31.6)	2661 (33.1)	2093 (36.0)	2116 (36.3)
	Total	8266	8049	5807	5829

[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 1.2.1.1 and 1.2.1.2

As of the data cut-off date of 04 November 2020, 5807 participants in the AZD1222 group for the SDSD + LDSD Seronegative for Efficacy Analysis Set had a median duration of follow-up from 15 days post second dose (ie, endpoint for primary efficacy endpoint) of 48.0 days (range, 1 to 79 days) and from first dose of 132.0 days (range, 41 to 158 days); 5829 participants in the control group had a median duration of follow-up from 15 days post second dose of 48.0 days (range, 1 to 79 days) and from first dose of 133.0 days (range, 35 to 158 days) (main efficacy Table 1.4.12.1).

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:

- 6% of participants were ≥ 65 years of age and mean age was approximately 42 years old
- 61% of participants were female
- 83% of participants were White, 4% were Black, 5% were other, 4% were Asian
- 36% of participants had a comorbidity at baseline

Demographics and baseline characteristics for the SDSD + LDSD Immunogenicity Analysis Set were not entirely consistent with the efficacy analysis sets, as it was enriched for older adults, the AZD1222 group, and diversity with regard to country (UK, Brazil, and South Africa), which also increased diversity in race. As noted previously, South Africa was not included in the efficacy analyses. Overall, in the SDSD + LDSD Immunogenicity Analysis Set (see Immuno Tables 1.1.3.4 and 1.1.4.4), approximately:

- 15% of participants were ≥ 65 years of age and mean age was approximately 46 years old
- 53% of participants were female
- 76% of participants were White, 12% were Black, 7% were other, 4% were Asian
- 37% of participants had a comorbidity at baseline

4.2.2 Efficacy Against COVID-19

Definitions of the primary endpoint and secondary endpoints are provided in Table 5. All SARS-CoV-2 virologically confirmed results were adjudicated and classified according to the WHO severity grading scale in Table 5. The adjudicated results were used for the pooled interim analyses.

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

The vaccine efficacy of AZD1222 was 70.42% (95.84% CI: 54.84%, 80.63%) ($p < 0.001$) against COVID-19 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).

A supportive analysis of the primary endpoint restricting the population to those confirmed to have received SDSD provided similar results to those observed for the primary analysis (Table 8).

In an exploratory subgroup analysis of the primary endpoint restricting the population to those confirmed to have received LDSD, efficacy of the AZD1222 vaccine was 90.05% (95.84% CI: 65.84%, 97.10%) against COVID-19. This dosing regimen subgroup is discussed further in Section 4.2.8.

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

	Participants with events						
	AZD1222		Control		VE	95.84% CI	
Analysis population	N	n (%)	N	n (%)	(%)	(%)	P-value
Primary endpoint: SDSD + LDSD, seronegative	5807	30 (0.52)	5829	101 (1.73)	70.42	(54.84, 80.63)	<0.001
SDSD + LDSD ITT, seronegative	5814	31 (0.53)	5831	100 (1.71)	69.13	(53.10, 79.68)	<0.001
SDSD, seronegative	4440	27 (0.61)	4455	71 (1.59)	62.10	(39.96, 76.08)	<0.001
LDSD, seronegative	1367	3 (0.22)	1374	30 (2.18)	90.05	(65.84, 97.10)	<0.001

VE of AZD1222 versus control, the 95.84% 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 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 of the infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95.84% CI for the VE was obtained by taking 1 minus the 95.84% CI of the risk ratio derived from the model.

For the primary endpoint efficacy objective to be met, the lower bound of the CI for the VE must be > 20%.

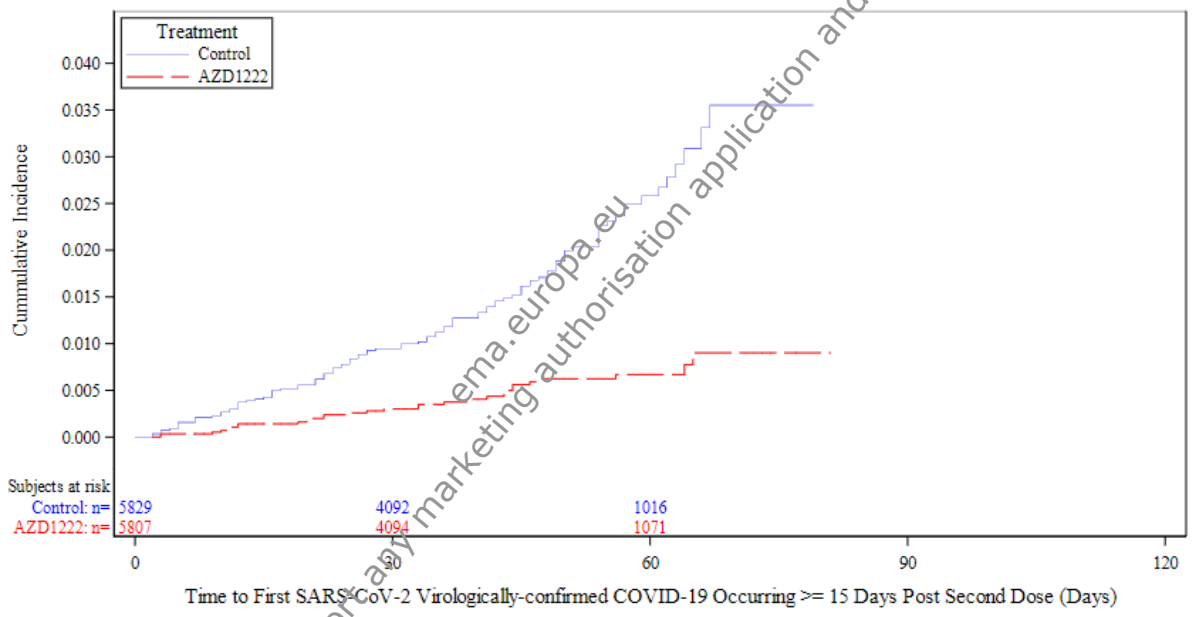
The observation period for the endpoint was 15 days post second dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events.

Source: Main Efficacy Tables 1.3.1.1, 1.3.1.2, 1.3.1.3, and 1.3.1.4.

A supportive analysis of the primary endpoint using the Cox Proportional Hazard model and the SDSD + LDSD Seronegative for Efficacy Analysis Set provided similar results to those observed for the primary analysis with a vaccine efficacy of 70.60% and 95% CI of 56.41%, 80.77% (see Main Efficacy Table 1.3.2.1). 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.

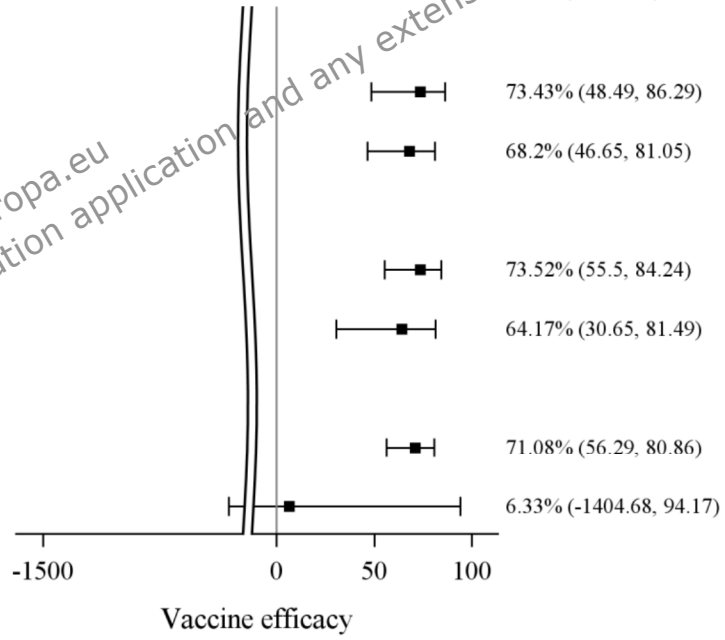
COVID-19 endpoints are based on adjudicated events.

Source: Main Efficacy Figure 1.3.2.1.

Subgroup analyses of the primary endpoint showed efficacy of the AZD1222 vaccine against COVID-19 for the subgroup categories of comorbidity, age, and country that was consistent with the primary endpoint, except for older adults (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)**

Subgroup	AZD122 (N=5807) Number of Participants	AZD122 (N=5807) Observed Events	Control (N=5829) Number of Participants	Control (N=5829) Observed Events	Vaccine efficacy (95% CI)
Comorbidity at Baseline					
Yes	2070	11 (0.53)	2133	43 (2.02)	73.43% (48.49, 86.29)
No	3733	19 (0.51)	3683	58 (1.57)	68.2% (46.65, 81.05)
Country					
United Kingdom	3744	18 (0.48)	3804	68 (1.79)	73.52% (55.5, 84.24)
Brazil	2063	12 (0.58)	2025	33 (1.63)	64.17% (30.65, 81.49)
Age group at screening					
18-64 years	5466	29 (0.53)	5510	100 (1.81)	71.08% (56.29, 80.86)
65 years and above	341	1 (0.29)	319	1 (0.31)	6.33% (-1404.68, 94.17)



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 of the infection from the AZD1222 arm / incidence of infection 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: Age Efficacy Figure 4.3.3.1.

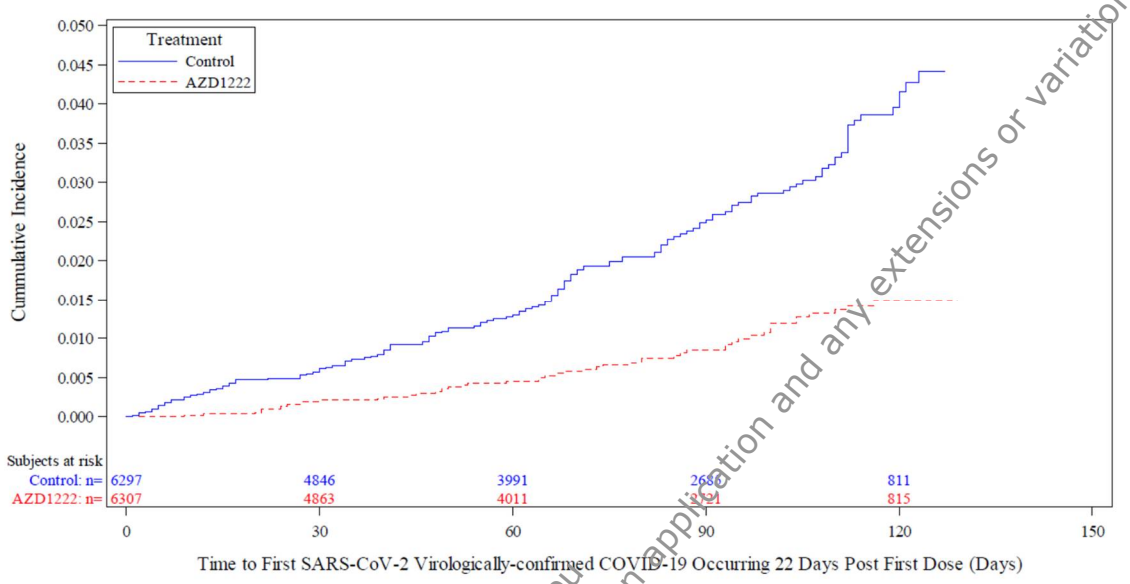
4.2.2.2 Efficacy Against COVID-19 Following First Dose

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 64.07% (95% CI: 50.53%, 73.90%) (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).

Similarly, the vaccine efficacy in participants seronegative at baseline who received a LD as the first dose with follow up ≥ 22 days post first dose was 70.15% (95% CI: 43.22%, 84.30%) (see Main Efficacy Table 1.4.10.2).

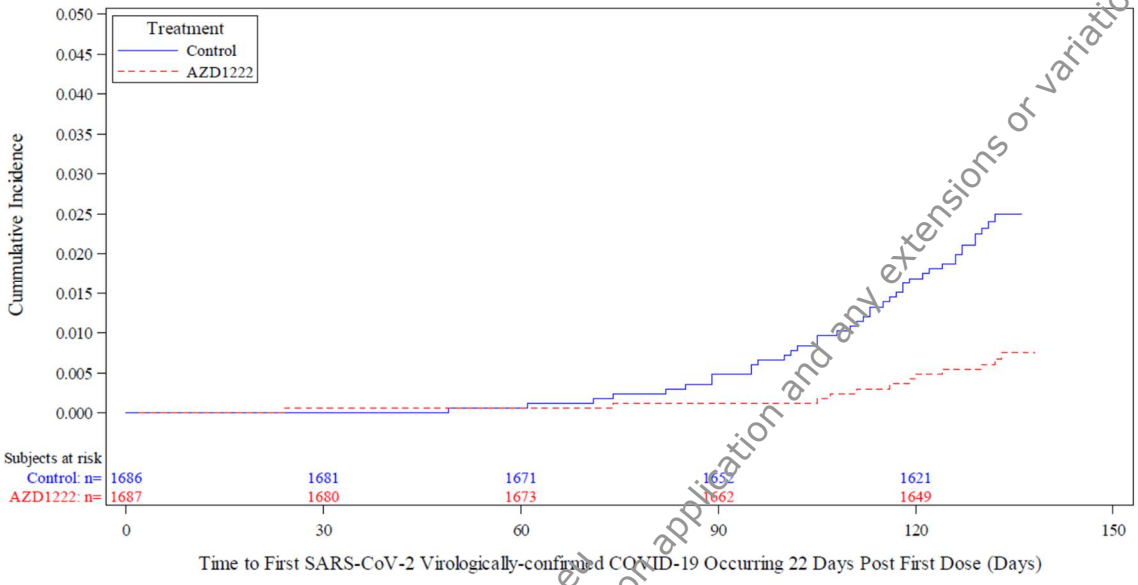
A Cumulative Incidence curve of the time to first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥ 22 days post first dose shows divergence of the curve for the AZD1222 group (Dose 1 SD seronegative group) from the control group following the first dose (Figure 5). A Cumulative Incidence curve for the corresponding Dose 1 LD seronegative group shows that the curve for the AZD1222 group does not diverge until approximately 75 days after the first dose (Figure 6) due to low incidence of disease in this numerically smaller group. Protection after first dose is further explored for both the SD and LD in Section 4.2.9.3.

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.

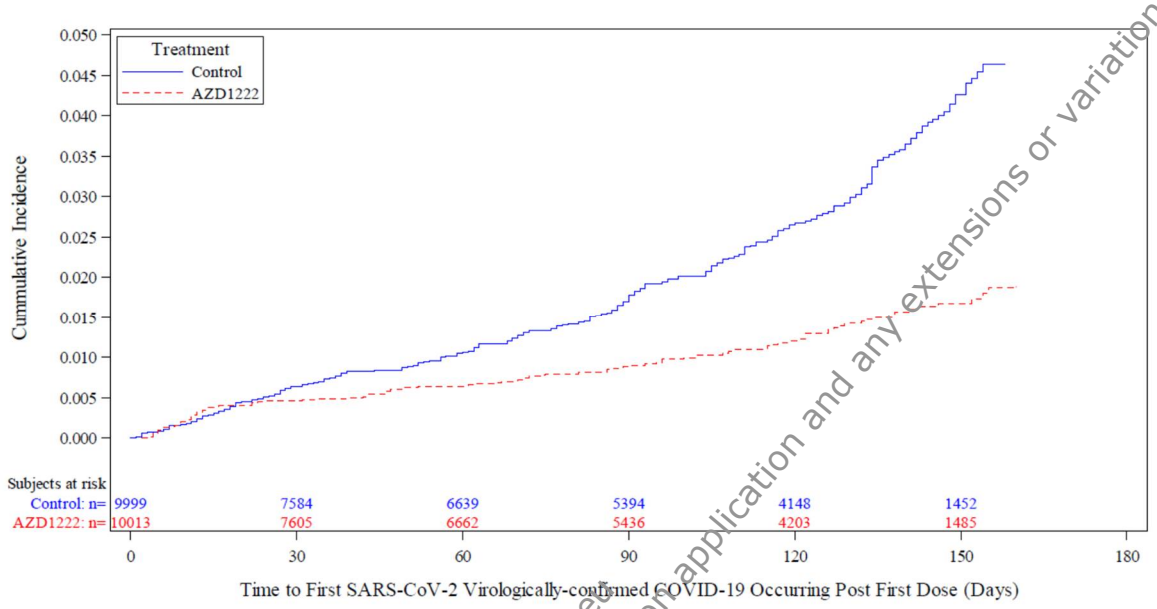
Figure 6 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed COVID-19 Occurring 22 Days Post First Dose of Study Intervention (Dose1 LD Seronegative for Efficacy Analysis Set)



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 1.4.11.2.

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 was 52.69% (95% CI: 40.52%, 62.37%) against COVID-19 in this group of participants (Table 23). Examination of the Cumulative Incidence curves in Figure 7 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 7 **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

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

As of the data cut off on 04 November 2020, limited follow up time and a limited number of cases of COVID-19 hospitalisation admissions and severe COVID-19 disease had accumulated in the pooled efficacy population; however, there was a consistent trend of vaccine efficacy against severe cases of COVID19.

The AZD1222 vaccine provided protection against COVID-19 hospital admission (WHO Severity Grading ≥ 4) evaluated 22 days after the first dose. The incidence of COVID-19 hospital admission ≥ 22 days post first dose was lower in seronegative participants who received AZD1222 SD for the first dose than those who received control (0 vs 9) (Table 9).

Among the 10000 control recipients in the Any Dose for Efficacy Analysis Set with follow up post first dose, there were 16 cases of COVID-19 hospital admissions and 2 severe COVID-19

cases, one of which was fatal. In contrast, among the 10014 AZD1222-treated participants, there were only 2 cases of COVID-19 hospital admissions and no cases of severe COVID-19. (see Main Efficacy Tables 1.4.8.1, 1.4.2.1, 1.4.14.1, 1.4.20.1, and 1.4.17.1). 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 8).

Table 9 Vaccine Efficacy Against COVID-19 Hospital Admissions

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	5807	0	5829	5 (0.09)	100 [a]	(-9.44, NE) [a]	0.063 [a]
Dose 1 SD, seronegative	≥ 22 days post first dose	6307	0	6297	9 (0.14)	100 [a]	(49.55, NE) [a]	0.004 [a]
Dose 1 LD, seronegative	≥ 22 days post first dose	1687	0	1686	1 (0.06)	100 [a]	(-3797.69, NE) [a]	>0.999 [a]
Any dose	Post first dose	10014	2 (0.02) [c]	10000	16 (0.16)	87.59 [b]	(46.03, 97.15) [b]	0.005 [b]

[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 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.

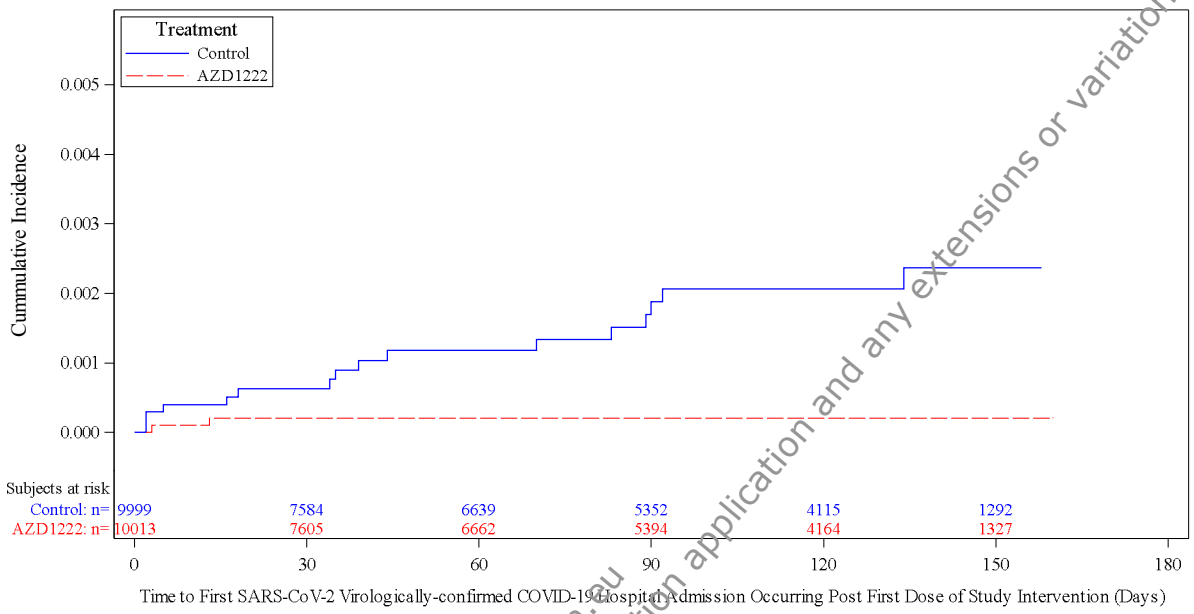
[c] VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1-(incidence of the infection from the AZD1222 arm / incidence of infection 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.

[d] 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, see Table 5.

Source: Main Efficacy Tables 1.4.13.1, 1.4.14.1, 1.4.15.1, and 1.4.15.2.

Figure 8 **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, 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-19 endpoints are based on adjudicated events.

Source: Supplemental Figure IEMT35.

There was a trend for protection against severe COVID-19, referring to all case definitions with a WHO severity grading ≥ 6, in participants who received AZD1222, although the number of cases was too low to inferentially assess vaccine efficacy. The incidence of COVID-19 cases occurring ≥ 22 days post first dose are shown in Table 10 for the Dose 1 SD Seronegative for Efficacy Analysis.

Table 10 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 22 Days Post First Dose (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=6307)	Control (N=6297)			
COVID-19 (primary case definition)	51 (0.81)	141 (2.24)	64.07[a]	(50.53, 73.90) [a]	<0.001 [a]
COVID-19 hospitalisation	0	9 (0.14)	100[b]	(49.55, NE) [b]	0.004 [b]
COVID-19 severe disease	0	1 (0.02)	100[b]	(-3808.49, NE) [b]	>0.999 [b]
COVID-19 requiring ICU	0	1 (0.02)	100[b]	(-3808.49, NE) [b]	>0.999 [b]
COVID-19 death	0	1 (0.02)	100[b]	(-3808.49, NE) [b]	>0.999 [b]

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

The observation period for the endpoint was from 22 days post first dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events. Severity of COVID-19 events was defined using the 10-point WHO clinical progression scale shown in Table 5.

Source: Main Efficacy Tables 1.4.3.1, 1.4.10.1, 1.4.15.1, 1.4.18.1, and 1.4.21.1.

The same trend for vaccine protection against COVID-19 hospitalisation and severe COVID-19 was observed in the Dose 1 LD Seronegative for Efficacy recipients (Table 11).

Table 11 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 22 Days Post First Dose (Dose 1 LD 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=1687)	Control (N=1686)			
COVID-19 (primary case definition)	12 (0.71)	40 (2.37)	70.15 [a]	(43.22, 84.30) [a]	<0.001 [a]
COVID-19 hospitalisation	0	1 (0.06)	100 [b]	(-3797.69, NE) [b]	>0.999 [b]
COVID-19 severe disease	0	1 (0.06)	100 [b]	(-3797.69, NE) [b]	>0.999 [b]
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

The observation period for the endpoint was from 22 days post first dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events. Severity of COVID-19 events was defined using the 10-point WHO clinical progression scale shown in Table 5.

Source: Main Efficacy Tables 1.4.3.2, 1.4.10.2, 1.4.15.2, 1.4.18.2, and 1.4.21.2.

4.2.4 Efficacy on Asymptomatic SARS-CoV-2 Infection

In the COV002 study, 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'.

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, 1.4.6.1, and 1.4.6.2). When grouping participants with asymptomatic infection or in whom the occurrence of symptoms were unknown, there was a trend observed in the LDSD group for efficacy

against any SARS-CoV-2 infection (59.03%; 95% CI: 1.40%, 82.97%), but not in the SDSD group (3.94%; 95% CI: −72.14%, 46.4%) (Table 12).

Table 12 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 for COV002, seronegative	Asymptomatic SARS-CoV-2 infection	2377	8 (0.34)	2430	11 (0.45)	26.94	(-81.50, 70.59)	0.499
	Asymptomatic or unknown symptoms SARS-CoV-2 infection	2377	22 (0.93)	2430	23 (0.95)	3.94	(-72.14, 46.40)	0.892
LDSD for COV002, seronegative	Asymptomatic SARS-CoV-2 infection	1367	3 (0.22)	1374	9 (0.66)	66.83	(-22.32, 91.01)	0.097
	Asymptomatic or unknown symptoms SARS-CoV-2 infection	1367	7 (0.51)	1374	17 (1.24)	59.03	(1.40, 82.97)	0.046

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 of the infection from the AZD1222 arm/ incidence of infection 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 15 days post second dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events.

Source: Main Efficacy Tables 1.4.4.2, 1.4.4.3, 1.4.24.2, and 1.4.24.3.

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

As discussed in Section 1.3, comorbid conditions such as cardiovascular disease, respiratory disease, or type 2 diabetes are risk factors for COVID-19 disease progression, associated complications, and death. These conditions, as well as a BMI ≥ 30 kg/m^2, defined the prespecified comorbid conditions subgroup.

Approximately 36% of participants in the primary efficacy population, as well as of the overall study population, had at least one comorbidity at baseline. The demography of these participants with comorbid conditions was consistent between the two study populations. The most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%).

The AZD1222 vaccine provided protection against COVID-19 in adults with comorbid conditions that was consistent with the level of protection in the general study population. Vaccine efficacy estimates across the range of COVID-19 disease severity is shown from ≥ 15 days post second dose (Table 13) and from ≥ 22 days after the first SD (Table 14).

Table 13 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 15 Days Post Second Dose in Adults with a Comorbid Condition at Baseline (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 (N=2070)	Control (N=2133)			
COVID-19 (primary case definition)	11 (0.53)	43 (2.02)	73.43 [a]	(48.49, 86.29) [a]	<0.001 [a]
COVID-19 hospitalisation	0	3 (0.14)	100 [b]	(-149.36, NE) [b]	0.261 [b]
COVID-19 severe disease	0	1 (0.05)	100 [b]	(-3918.70, NE) [b]	>0.999 [b]
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

Comorbidities at baseline = Yes if any comorbidity (BMI ≥ 30 kg/m^2 at baseline, cardiovascular disorder, respiratory disease or diabetes) is Yes.

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: Comorbidity Tables 2.3.1.1.a, 2.4.13.1.a, 2.4.1.1.a, 2.4.19.1.a, and 2.4.16.1.a.

Table 14 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 22 Days Post First Dose in Adults with Comorbid Conditions (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=2322)	Control (N=2382)			
COVID-19 (primary case definition)	19 (0.82)	60 (2.52)	66.10 [a]	(43.27, 79.75) [a]	<0.001 [a]
COVID-19 hospitalisation	0	4 (0.17)	100 [b]	(-55.40, NE) [b]	0.132 [b]
COVID-19 severe disease	0	0	-	-	-
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

Comorbidities at baseline = Yes if any comorbidity (BMI ≥ 30 kg/m^2 at baseline, cardiovascular disorder, respiratory disease or diabetes) is Yes.

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: Comorbidity Tables 2.4.3.1.a, 2.4.10.1.a, 2.4.15.1.a, 2.4.18.1.a, and 2.4.21.1.a.

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

As of the data cut-off on 04 November 2020, a low number of older adults ≥ 65 years of age (660 total participants) were enrolled and included in the primary efficacy population (SDSD + LDSD Seronegative for Efficacy Analysis Set) (N = 341 for AZD1222 and N = 319 for control) (see Age Safety Table 4.1.3.2.b). There was also limited follow up time available for this group of older adults in the pooled efficacy analysis. The median duration of follow up

after the first dose was 71.0 days and 15 days after the second dose was 20.0 days (see Age Efficacy Table 4.4.12.1). A large proportion (85%) of older adults received their second dose <6 weeks after their first (see Age Safety Table 4.2.1.1b).

A limited number of COVID-19 cases had accumulated at the time of the data cut-off. The total number of COVID-19 cases in the full efficacy population (Any Dose for Efficacy Analysis Set) that occurred any time after the first dose was 10, with 2 (0.21%) in the AZD1222 group and 8 (0.89%) in the Control group (Table 15). In the AZD1222 vaccine group, no COVID-19 hospitalisations or severe COVID-19 cases were reported in older adults, whereas in the Control group, 2 of the 8 cases required hospitalisation.

These early data suggest that the AZD1222 vaccine provides protection against COVID-19 in older adults that is consistent with the general study population.

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

COVID-19 case definition	Participants with events, n (%)		VE (%)	95%[a] or 97.5%[b] CI	Nominal p-value
	AZD1222 (N = 950)	Control (N= 894)			
COVID-19 (primary case definition)	2 (0.21)	8 (0.89)	76.43 [a]	(-11.01, 94.99) [a]	0.068 [a]
COVID-19 hospitalisation	0	2 (0.22)	100 [b]	(-401.07, NE) [b]	0.470 [b]
COVID-19 severe disease	0	0	-	-	-
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

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 4.4.2.1.b, 4.4.8.1.b, 4.4.14.1.b, 4.4.17.1.b, and 4.4.20.1.b

4.2.7 Efficacy by Country

For the primary efficacy analysis population (SDSD + LDSD, seronegative), the baseline characteristics were comparable for participants in the UK and Brazil. Some differences were observed with regards to demographics, particularly for age and race. Participants in the UK were slightly older, with a median age of 42 years (range, 18 to PPD years) and 7.4% of participants ≥ 65 years of age, when compared with participants in Brazil, with a median age of 37 years (range, PPD to PPD years) and 3.1% of participants ≥ 65 years of age. The percentage of White participants was higher in the UK (92.1%) than Brazil (65.8%). In general, Brazil had a more racially diverse population, with 12.6% Other, 11.11% Black, and 7.7% mixed (see Country Efficacy Tables 3.1.3.2.a and 3.1.3.2.b).

The dose interval and dose levels for the primary efficacy analysis population were also different between the 2 countries. Participants in the UK had a longer dose interval than participants in Brazil: 51.5% of participants in the UK had a dose interval ≥ 12 weeks (8.0% in Brazil), whereas, 60.5% of participants in Brazil had a dose interval < 6 weeks (12.1% in the UK). In the UK, approximately two-thirds of participants (63.5%) received SDSD and one-third (36.5%) received LDSD; in Brazil, all participants received SDSD (see Country Safety Tables 3.2.1.2a and 3.2.1.2.b).

In both countries, 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. The vaccine efficacy was generally similar for the UK and Brazilian populations (Table 16).

Table 16 Vaccine Efficacy for Incidence of COVID-19 Cases Occurring ≥ 15 Days Post Second Dose in Adults in UK and Brazil (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 = 3744**	**N= 3804**			
COVID-19 (primary case definition)	18 (0.48)	68 (1.79)	73.52 [a]	(55.50, 84.24) [a]	<0.001 [a]
COVID-19 hospitalisation	0	2 (0.05)	100 [b]	(-440.99, NE) [b]	0.508 [b]
COVID-19 severe disease	0	1 (0.03)	100 [b]	(-3862.50, NE) [b]	>0.999 [b]
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-
BRAZIL	**N = 2063**	**N = 2025**			
COVID-19 (primary case definition)	12 (0.58)	33 (1.63)	64.17 [a]	(30.65, 81.49) [a]	0.002 [a]
COVID-19 hospitalisation	0	3 (0.15)	100 [b]	(-137.54, NE) [b]	0.243 [b]
COVID-19 severe disease	0	0	-	-	-
COVID-19 requiring ICU	0	0	-	-	-
COVID-19 death	0	0	-	-	-

[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 of the infection from the AZD1222 arm / incidence of infection 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 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 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.

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 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.

4.2.8 Humoral Immunogenicity

Humoral immunogenicity was analysed using a validated multiplexed immunoassay in which the quantitative expression of Spike and RBD responses was 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, as well as to have a larger proportion of AZD1222 participants. 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. All data discussed in this section are for seronegative participants at baseline, unless otherwise stated.

The results presented in this section show that 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 was ≥ 98% at 28 days after the first dose and > 99% 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 (see Immuno Tables 1.7.2.1.1, 1.7.2.1.2, and 1.7.2.1.3). 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 (see Immuno Tables 1.7.2.3.1, 1.7.2.3.2, and 1.7.2.3.3). 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

For seronegative participants at baseline in the combined (SDSD + LDSD) immunogenicity analysis set, an increase in S-binding antibodies was observed at 28 days after the first dose (GMFR = 143.4) with a notable further increase at 28 days following the second dose (GMFR = 524.3) (Table 17 and see Immuno Table 1.7.1.1.1).

Of note, baseline seropositive participants also had increased S-binding responses after a first dose, with a GMFR = 12.8 (95% CI: 7.0, 23.5) over baseline values. 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 that suggest 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 prior to the widespread availability of vaccines (Moscola et al 2020).

Geometric mean titres for S-binding antibodies in the SDSD analysis set (baseline seronegative participants) were numerically higher after the first dose compared with the GMT for the LDSD analysis set (Table 17). Pseudoneutralisation assay titres for nAb were similar between the dose levels after the first dose (Table 18).

Following the second dose, GMT further increased for both SDSD and LDSD analysis sets, with a numerically higher GMT for the LDSD regimen (Table 17). This increased response for the LDSD regimen was consistent across assays for nAb (pseudoneutralisation [Table 18] and live nAb [see Immuno Table 1.7.1.3.3]) and anti-RBD (see Immuno Table 1.7.1.2.3).

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

No differences in immunogenicity were observed in the subcategory of participants with comorbidity compared with those without comorbidity, when examining binding antibody (Table 17) and nAb GMTs (Table 18) after both the first dose and second dose. Responses analysed in a live neutralisation assay confirmed this finding, with GMTs = 185.36, 594.53 AU/mL after first and second dose of AZD1222 in the SDSD + LDSD analysis set with no comorbidity and GMT = 169.52, 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).

Country

Similar levels of S-binding antibody were induced after the first dose in UK, Brazil, and South Africa (Table 17) 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 (Table 18). Comparisons between UK and Brazil may be confounded by dose interval (see Supplemental Tables IEMT46.1.1.2.a through IEMT46.1.4.3.d). The nAb titres by pseudoneutralisation in South Africa were high, which may be a result of low numbers of study participants analysed at the point of data cut off.

Given that the vaccine efficacy against COVID-19 in the SDSD set in Brazil was similar to that observed in the SDSD set in the UK (64.17% and 60.35%; see Country Efficacy Tables 3.3.1.2.a and 3.3.1.2.b), the differences in induction of S-binding antibodies observed at a country-specific level appear not to be clinically meaningful.

Older Adults (≥ 65 years of age)

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 (Table 17). Similarly, nAb (pseudoneutralisation) GMTs were lower in the older adults (Table 18).

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). The current report differs in that validated assays have been utilised, the sample size is larger and draws from a broader population that includes older adults with comorbidity. 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 4.2.9.2 and Table 20).

The titres for S-binding antibodies observed in the older adults were similar to the titres in Brazilian participants (see discussion under Country in Section 4.2.8 and Table 17) for whom the vaccine efficacy was 64.17%, which was consistent with the efficacy observed for all other subgroups (Figure 4). While absolute titres of binding and neutralising antibody tended to be lower in older adults, the clinical significance of this observation is currently unknown.

Table 17 Quantification of SARS-CoV-2 S-binding Antibody Levels by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	SDSD + LDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
SEROSTATUS		N	1655	1197	1356	299
Seronegative	Post Dose 1	n / N_{sub}	885 / 1617	704 / 1166	817 / 1320	68 / 297
		GMT	**8156.07**	**56.85**	**8386.46**	**5836.18**
		(95% CI)	(7563.3, 8795.3)	(51.6, 62.6)	(7758.6, 9065.1)	(4340.4, 7847.4)
	Post Dose 2	n / N_{sub}	886 / 1617	705 / 1166	819 / 1320	67 / 297
		GMT	**30206.20**	**62.70**	**29034.74**	**48986.76**
		(95% CI)	(28271.0, 32273.9)	(56.3, 69.8)	(27118.2, 31086.7)	(38483.3, 62357.0)
Seropositive	Post Dose 1	n / N_{sub}	29 / 38	28 / 31	28 / 36	1 / 2
		GMT	**178522.42**	**7303.99**	**175120.84**	**305936.00**
		(95% CI)	(123872.3, 257283.1)	(3307.9, 16127.4)	(120096.9, 255354.8)	(NE, NE)
	Post Dose 2	n / N_{sub}	29 / 38	25 / 31	28 / 36	1 / 2
		GMT	**114488.67**	**8296.39**	**112978.13**	**166062.00**
		(95% CI)	(74664.2, 175554.8)	(4233.6, 16258.1)	(72553.8, 175925.4)	(NE, NE)
COMORBIDITY [a]		N	1532	1114	1235	297
Yes	Post Dose 1	n / N_{sub}	324 / 594	279 / 440	305 / 496	19 / 98
		GMT	**7881.34**	**59.61**	**8029.71**	**5842.12**
		(95% CI)	(6917.0, 8980.1)	(50.6, 70.2)	(7043.9, 9153.5)	(2660.5, 12828.4)
	Post Dose 2	n / N_{sub}	308 / 594	275 / 440	290 / 496	18 / 98
		GMT	**28379.38**	**59.38**	**27492.25**	**47338.76**
		(95% CI)	(25423.2, 31679.3)	(50.0, 70.5)	(24536.1, 30804.6)	(32020.3, 69985.6)

Table 17 Quantification of SARS-CoV-2 S-binding Antibody Levels by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	SDSD + LDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
No	Post Dose 1	n / N_{sub}	492 / 938	385 / 674	443 / 739	49 / 199
		GMT	**8296.10**	**55.86**	**8625.58**	**5833.88**
		(95% CI)	(7512.3, 9161.7)	(49.3, 63.3)	(7767.0, 9579.1)	(4322.2, 7874.2)
	Post Dose 2	n / N_{sub}	509 / 938	390 / 674	460 / 739	49 / 199
		GMT	**27784.52**	**65.64**	**26120.87**	**49606.46**
		(95% CI)	(25502.4, 30270.9)	(56.5, 76.2)	(23929.4, 28513.0)	(36571.6, 67287.1)
COUNTRY [a]		N	1617	1166	1320	297
UK	Post Dose 1	n / N_{sub}	575 / 1114	404 / 681	510 / 820	65 / 294
		GMT	**7322.20**	**43.12**	**7548.08**	**5769.13**
		(95% CI)	(6675.7, 8031.3)	(38.6, 48.2)	(6853.0, 8313.7)	(4237.7, 7854.0)
	Post Dose 2	n / N_{sub}	542 / 1114	367 / 681	478 / 820	64 / 294
		GMT	**34156.88**	**47.50**	**32384.99**	**50846.74**
		(95% CI)	(31333.9, 37234.2)	(41.7, 54.1)	(29560.8, 35479.0)	(39660.8, 65187.6)
Brazil	Post Dose 1	n / N_{sub}	208 / 394	199 / 380	208 / 394	-
		GMT	**10013.29**	**81.09**	**10013.29**	**-**
		(95% CI)	(8504.8, 11789.3)	(68.4, 96.2)	(8504.8, 11789.3)	-
	Post Dose 2	n / N_{sub}	238 / 394	235 / 380	238 / 394	-
		GMT	**22305.42**	**79.72**	**22305.42**	**-**
		(95% CI)	(19905.8, 24994.3)	(66.8, 95.2)	(19905.8, 24994.3)	-

Table 17 Quantification of SARS-CoV-2 S-binding Antibody Levels by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	SDSD + LDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
South Africa	Post Dose 1	n / N_{sub}	102 / 109	101 / 105	99 / 106	3 / 3
		GMT	**9859.17**	**85.25**	**9941.36**	**7496.44**
		(95% CI)	(8026.4, 12110.5)	(60.7, 119.7)	(8050.6, 12276.2)	(1461.4, 38454.7)
	Post Dose 2	n / N_{sub}	106 / 109	103 / 105	103 / 106	3 / 3
		GMT	**31828.30**	**97.45**	**32167.36**	**22121.36**
		(95% CI)	(26174.5, 38703.3)	(66.1, 143.6)	(26317.7, 39317.2)	(8547.7, 57250.2)
AGE [a]		N	1617	1166	1320	269
Age 18-64	Post Dose 1	n / N_{sub}	745 / 1373	567 / 994	677 / 1104	68 / 269
		GMT	**8610.76**	**61.87**	**8953.81**	**5836.18**
		(95% CI)	(7927.3, 9353.2)	(55.4, 69.0)	(8218.3, 9755.1)	(4340.4, 7847.4)
	Post Dose 2	n / N_{sub}	770 / 1373	598 / 994	703 / 1104	67 / 269
		GMT	**31969.52**	**68.07**	**30695.30**	**48986.76**
		(95% CI)	(29763.6, 34338.9)	(60.3, 76.8)	(28496.2, 33064.1)	(38483.3, 62357.0)
Age ≥65	Post Dose 1	n / N_{sub}	140 / 244	137 / 172	140 / 216	-
		GMT	**6110.88**	**40.04**	**6110.88**	**-**
		(95% CI)	(5111.6, 7305.6)	(33.2, 48.3)	(5111.6, 7305.6)	-
	Post Dose 2	n / N_{sub}	116 / 244	107 / 172	116 / 216	-
		GMT	**20727.02**	**39.59**	**20727.02**	**-**
		(95% CI)	(17646.6, 24345.2)	(32.4, 48.4)	(17646.6, 24345.2)	-

[a] Data are shown for the seronegative at baseline participants for comorbidity, country, and age subgroups.
Participants with indeterminate and missing value of baseline serostatus are not included. Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention.
Titre values measured as below LLoQ (33) are imputed to a value that is half of the LLoQ. Titre values measured as above ULoQ (2000000) are imputed at the ULoQ value.

N = number of participants overall in the subgroup category; Nsub = number of participants in each subgroup per treatment group; n = number of participants with a sample included in the assay at that time point.
Source: Immuno Tables 1.7.1.1.1, 1.7.1.1.2, and 1.7.1.1.3 (Serostatus); Immuno Tables 2.7.1.1.1.a, 2.7.1.1.1.b, 2.7.1.1.2.a, 2.7.1.1.1.b, 2.7.1.1.3a, and 2.7.1.1.3.b (Comorbidity); Immuno Tables 3.7.1.1.1.a, 3.7.1.1.b, 3.7.1.1. 1.c, 3.7.1.1.2.a, 3.7.1.2.1.b, 3.7.1.1.2.c, 3.7.1.1.3.a, 3.7.1.1.3.b, and 3.7.1.1.3.c (Country); Immuno Tables 4.7.1.1.1.a, 4.7.1.1.1.b, 4.7.1.1.2.a, 4.7.1.1.2.b, 4.7.1.1.3.a, and 4.7.1.1.3.b (Age).

Table 18 Quantification of SARS-CoV-2 nAbs Levels (by Pseudoneutralisation Assay) by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	LDSD + SDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
SEROSTATUS		N	1655	1197	1356	299
Seronegative	Post Dose 1	n / N_{sub}	720 / 1617	599 / 1166	575 / 1320	145 / 297
		GMT	**55.469**	**20.466**	**55.557**	**55.120**
		(95% CI)	(50.61, 60.80)	(20.04, 20.91)	(50.21, 61.47)	(44.35, 68.51)
	Post Dose 2	n / N_{sub}	703 / 1617	555 / 1166	549 / 1320	154 / 297
		GMT	**175.066**	**21.446**	**166.238**	**210.528**
		(95% CI)	(160.59, 190.84)	(20.68, 22.24)	(150.42, 183.72)	(178.31, 248.57)
Seropositive	Post Dose 1	n / N_{sub}	13 / 38	7 / 31	12 / 36	1 / 2
		GMT	**1663.063**	**51.748**	**1651.654**	**1806.288**
		(95% CI)	(1084.40, 2550.53)	(15.94, 168.05)	(1032.98, 2640.87)	(NE, NE)
	Post Dose 2	n / N_{sub}	13 / 38	5 / 31	12 / 36	1 / 2
		GMT	**887.206**	**71.497**	**919.414**	**578.339**
		(95% CI)	(594.92, 1323.10)	(14.48, 353.02)	(597.78, 1414.11)	(NE, NE)
COMORBIDITY [a]		N	1535	1114	1235	297
Yes	Post Dose 1	n / N_{sub}	266 / 594	237 / 440	218 / 496	48 / 98
		GMT	**54.494**	**20.531**	**51.549**	**70.133**
		(95% CI)	(46.70, 63.59)	(19.76, 21.34)	(43.80, 60.67)	(45.28, 108.62)
	Post Dose 2	n / N_{sub}	244 / 594	224 / 440	193 / 496	51 / 98
		GMT	**150.094**	**21.965**	**138.958**	**200.941**
		(95% CI)	(128.00, 176.00)	(20.55, 23.48)	(115.79, 166.76)	(145.75, 277.03)

Table 18 Quantification of SARS-CoV-2 nAbs Levels (by Pseudoneutralisation Assay) by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	LDSD + SDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
No	Post Dose 1	n / N_{sub}	425 / 938	341 / 674	328 / 739	97 / 199
		GMT	**54.224**	**20.297**	**55.897**	**48.927**
		(95% CI)	(48.26, 60.92)	(19.86, 20.74)	(48.94, 63.84)	(38.29, 62.51)
	Post Dose 2	n / N_{sub}	424 / 938	309 / 674	321 / 739	103 / 199
		GMT	**179.771**	**21.183**	**169.626**	**215.444**
		(95% CI)	(161.85, 199.68)	(20.27, 22.13)	(149.89, 191.97)	(177.33, 261.75)
COUNTRY [a]		N	1617	1166	1320	297
UK	Post Dose 1	n / N_{sub}	495 / 1114	375 / 681	351 / 820	144 / 294
		GMT	**52.788**	**20.223**	**51.966**	**54.845**
		(95% CI)	(47.31, 58.90)	(19.91, 20.55)	(45.80, 58.97)	(44.07, 68.26)
	Post Dose 2	n / N_{sub}	494 / 1114	342 / 681	341 / 820	153 / 294
		GMT	**189.759**	**21.543**	**181.393**	**209.820**
		(95% CI)	(171.89, 209.48)	(20.50, 22.64)	(160.51, 205.00)	(177.54, 247.97)
Brazil	Post Dose 1	n / N_{sub}	212 / 394	203 / 380	212 / 394	-
		GMT	**59.863**	**20.760**	**59.863**	**-**
		(95% CI)	(50.50, 70.96)	(19.71, 21.87)	(50.50, 70.96)	-
	Post Dose 2	n / N_{sub}	192 / 394	193 / 380	192 / 394	-
		GMT	**134.562**	**21.167**	**134.562**	**-**
		(95% CI)	(112.56, 160.87)	(20.12, 22.26)	(112.56, 160.87)	-

Table 18 Quantification of SARS-CoV-2 nAbs Levels (by Pseudoneutralisation Assay) by Subgroups (Immunogenicity Analysis Sets)

Subgroup	Timepoint	Statistic	LDSD + SDSD		SDSD	LDSD
			AZD1222	Control	AZD1222	AZD1222
South Africa	Post Dose 1	n / N_{sub}	13 / 109	21 / 105	12 / 106	1 / 3
		GMT	**105.544**	**22.077**	**104.928**	**113.219**
		(95% CI)	(41.45, 268.73)	(17.97, 27.13)	(37.60, 292.80)	(NE, NE)
	Post Dose 2	n / N_{sub}	17 / 109	20 / 105	16 / 106	1 / 3
		GMT	**328.669**	**22.532**	**327.231**	**352.541**
		(95% CI)	(208.63, 517.77)	(17.56, 28.92)	(201.20, 532.20)	(NE, NE)
AGE [a]		N	1617	1166	1320	269
Age 18-64	Post Dose 1	n / N_{sub}	645 / 1373	522 / 994	500 / 1104	145 / 269
		GMT	**58.124**	**20.374**	**59.026**	**55.120**
		(95% CI)	(52.69, 64.12)	(19.99, 20.76)	(52.87, 65.90)	(44.35, 68.51)
	Post Dose 2	n / N_{sub}	651 / 1373	501 / 994	497 / 1104	154 / 269
		GMT	**181.790**	**21.487**	**173.708**	**210.528**
		(95% CI)	(166.36, 198.66)	(20.67, 22.33)	(156.52, 192.78)	(178.31, 248.57)
Age ≥65	Post Dose 1	n / N_{sub}	75 / 244	77 / 172	75 / 216	-
		GMT	**37.103**	**21.105**	**37.103**	**-**
		(95% CI)	(29.26, 47.05)	(18.96, 23.49)	(29.26, 47.05)	-
	Post Dose 2	n / N_{sub}	52 / 244	54 / 172	52 / 216	-
		GMT	**109.212**	**21.066**	**109.212**	**-**
		(95% CI)	(77.58, 153.73)	(18.98, 23.38)	(77.58, 153.73)	-

[a] Data are shown for the seronegative at baseline participants for comorbidity, country, and age subgroups. Participants with indeterminate and missing value of baseline serostatus are not included. Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention.

Titre values measured as below LLoQ (40) are imputed to a value that is half of the LLoQ. Titre values measured as above ULoQ (787339) are imputed at the ULoQ value.
N = number of participants overall in the subgroup category; Nsub = number of participants in each subgroup per treatment group; n = number of participants with a sample included in the assay at that time point.
Source: Immuno Tables 1.7.1.4.1, 1.7.1.4.2, and 1.7.1.4.3 (Serostatus); Immuno Tables 2.7.1.4.1.a, 2.7.1.4.1.b, 2.7.1.4.2.a, 2.7.1.4.1.b, 2.7.1.4.3a, and 2.7.1.4.3.b (Comorbidity); Immuno Tables 3.7.1.4.1.a, 3.7.1.4.b, 3.7.1.4.c, 3.7.1.4.2.a, 3.7.1.4.2.b, 3.7.1.4.2.c, 3.7.1.4.3.a, 3.7.1.4.3.b, 3.7.1.4.3.c, 4.7.1.4.1.a, 4.7.1.4.1.b, and 4.7.1.4.1.c (Country); Immuno Tables 4.7.1.4.2.a, 4.7.1.4.2.b, 4.7.1.4.3.a, and 4.7.1.4.3.b (Age).

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.

The LDSD efficacy analysis population consists of participants from the UK only (for Study COV002), whereas the SDSD efficacy analysis population is represented in both UK (Study COV002) and Brazil (Study COV003). The full demographic and baseline characteristics of recipients of an SDSD or LDSD regimen are broadly similar, but there are some key differences, in age, race, prevalence of comorbidity, dose interval and duration of follow up, which are presented by country in Table 19 below.

In this section, the results of an in-depth exploratory analysis of the pooled data set for efficacy is presented to assess the effect of dose level and dose interval on vaccine efficacy.

Table 19 Select Population Characteristics for LDSD and SDSD Seronegative Analysis Sets by Country

Parameter	Statistic	LDSD – UK		SDSD – UK		SDSD - Brazil	
		AZD1222 (N = 1367)	Control (N = 1374)	AZD1222 (N = 2377)	Control (N = 2430)	AZD1222 (N = 2063)	Control (N = 2025)
Age (years) at screening	Median	40.0	40.0	44.00	44.00	37.0	36.0
	≥ 65 years, n (%)	0	0	277 (11.7)	279 (11.5)	64 (3.1)	40 (2.0)
Race, n (%)	White	1261 (92.2)	1296 (94.3)	2189 (92.1)	2238 (92.1)	1357 (65.8)	1366 (67.5)
	Other	8 (0.6)	7 (0.5)	14 (0.6)	12 (0.5)	260 (12.6)	260 (12.8)
Comorbidity, n (%)	Yes	459 (33.6)	463 (33.7)	852 (35.8)	935 (38.5)	759 (36.8)	735 (36.3)
	No	908 (66.4)	909 (66.2)	1524 (64.1)	1492 (61.4)	1301 (63.1)	1282 (63.3)
Dose interval (weeks)	Median	12	12	10	10	5	5
Dose interval n(%)	< 6 weeks	0	0	453 (19.1)	454 (18.7)	1249 (60.5)	1244 (61.4)
	6-8 weeks	6 (0.4)	6 (0.4)	317 (13.3)	277 (11.4)	245 (11.9)	244 (12.0)
	9-11 weeks	388 (28.4)	378 (27.5)	653 (27.5)	718 (29.5)	403 (19.5)	392 (19.4)
	≥ 12 weeks	973 (71.2)	990 (72.1)	954 (40.1)	981 (40.4)	166 (8.0)	145 (7.2)
Duration of FU post dose 1 (days)	Median	154.0	154.0	136.0	136.0	100.0	99.0

Source: Country Safety Table 3.1.3.5.a, 3.1.3.5.b, 3.1.3.6.a, 3.1.4.5.a, 3.1.4.5.b, and 3.1.4.6.a; Country Efficacy Tables 3.4.12.2 and 3.4.12.3; Supplemental Tables IEMT26.3.1, IEMT26.3.2, and IEMT26.4 (dose interval).

4.2.9.1 Effect of Dose Level on Efficacy

Data from the LDSD and SDSD dose groups were pooled for the pre-specified primary analysis based on similar immunogenicity after a first LD or first SD based upon Spike-binding antibody data from a standardized Spike ELISA, in agreement with authorities.

As presented in Section 4.2.2.1, the point estimate of efficacy against COVID-19 was higher in the LDSD group than the SDSD group: 90.05% (95.84% CI: 65.84%, 97.10%) compared with 62.10% (95.84% CI: 39.96%, 76.08%). Geometric mean titres of the LDSD group were higher after two doses compared with the SDSD group across assays (Spike, RBD, pseudoneutralisation, live nAb). This finding is consistent with the higher level of efficacy observed in this group.

Potential mechanisms whereby a lower priming dose might lead to better protection from a second boosting dose include the potential for higher avidity CD4 T cell response or preferential switch B cell differentiation to long term memory cells rather than plasma cells (Billeskov et al 2017). The role of induction of lower levels of anti-vector antibodies cannot be ruled out, although 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 (Barrett et al 2020).

4.2.9.2 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 20). 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 (Table 21). The number of participants with available results in the LDSD is generally low, with particularly few results from participants with shorter dose intervals contributing. However, comparing SDSD and LDSD groups with the same interdose interval, the immune response post the second dose was similar.

This data is strongly suggestive that given that the median dose interval in the LDSD group was 12 weeks compared with 5 weeks in the SDSD group in Brazil and 10 weeks SDSD UK, that the higher levels of immunogenicity engendered in the LDSD group were influenced more by interval than by dose level.

Table 20 Quantification of SARS-CoV-2 Spike Antibody Levels for Different Regimens (Dose Level and Interval) (Seronegative at Baseline)

Visit Window	Statistic	SDSD AZD1222 < 6 wks N=677	SDSD AZD1222 6-8 wks N=239	SDSD AZD1222 9-11 wks N=169	SDSD AZD1222 ≥ 12 wks N=235	LDSD AZD1222 < 6 wks N=3	LDSD AZD1222 6-8 wks -	LDSD AZD1222 9-11 wks N=126	LDSD AZD1222 ≥ 12 wks N=168
Baseline	N	481	137	110	154	3	NA	30	35
	GMT	**60.51**	**58.02**	**48.79**	**52.98**	**50.92**	**NA**	**64.09**	**52.42**
	95% CI for GMT	(54.1, 67.7)	(46.3, 72.6)	(39.6, 60.1)	(44.4, 63.2)	(3.9, 669.2)	NA	(40.4, 101.6)	(37.7, 72.9)
	Min, Max	16.5, 71694.0	16.5, 7228.0	16.5, 4497.0	16.5, 827.0	16.5, 127.0	NA	16.5, 565.0	16.5, 304.0
Day 28 post the first dose	N	479	99	87	152	3	NA	30	35
	GMT	**8734.08**	**7295.54**	**7492.98**	**8618.17**	**7496.44**	**NA**	**4803.21**	**6750.27**
	95% CI for GMT	(7883.1, 9676.9)	(5857.4, 9086.7)	(5885.1, 9540.2)	(7195.4, 10322.3)	(1461.4, 38454.7)	NA	(3255.7, 7086.4)	(4184.6, 10889.0)
	Min, Max	16.5, 126108.0	426.0, 84533.0	46.0, 82133.0	93.0, 263135.0	3922.0, 14622.0	NA	268.0, 35010.0	51.0, 85889.0
Day 28 post the second dose	N	443	116	106	154	3	NA	29	35
	GMT	**22222.73**	**24363.10**	**34754.10**	**63181.59**	**22121.36**	**NA**	**36928.89**	**66274.91**
	95% CI for GMT	(20360.5, 24255.3)	(20088.5, 29547.3)	(30287.2, 39879.8)	(55180.1, 72343.4)	(8547.7, 57250.2)	NA	(24509.6, 55641.2)	(49546.6, 88651.1)
	Min, Max	101.0, 178580.0	40.0, 276501.0	3590.0, 579194.0	4612.0, 767654.0	14411.0, 30100.0	NA	3713.0, 559449.0	6456.0, 481664.0

Sources: Supplemental Tables IEMT46.1.1.2.a, IEMT46.1.1.2.b, IEMT46.1.1.2.c, IEMT46.1.1.2.d, IEMT46.1.1.3.a, IEMT46.1.1.3.c, and IEMT46.1.1.3.d.

Table 21 Quantification of nAbs (by Pseudoneutralisation Assay) Levels for Different Regimens (Dose Level and Interval) (Seronegative at Baseline)

Visit Window	Statistic	SDSD AZD1222 < 6 wks N=677	SDSD AZD1222 6-8 wks N=239	SDSD AZD1222 9-11 wks N=169	SDSD AZD1222 ≥ 12 wks N=235	LDSD AZD1222 < 6 wks N=3	LDSD AZD1222 6-8 wks -	LDSD AZD1222 9-11 wks N=126	LDSD AZD1222 ≥ 12 wks N=168
Baseline	N	246	131	100	152	1	NA	74	94
	GMT	**20.000**	**20.434**	**20.000**	**20.000**	**20.000**	**NA**	**20.000**	**20.000**
	95% CI for GMT	(NE, NE)	(19.58, 21.32)	(NE, NE)	(NE, NE)	(NE, NE)	NA	(NE, NE)	(NE, NE)
	Min, Max	20.00, 20.00	20.00, 333.72	20.00, 20.00	20.00, 20.00	20.00, 20.00	NA	20.00, 20.00	20.00, 20.00
Day 28 post the first dose	N	243	109	91	132	1	NA	64	80
	GMT	**50.565**	**53.040**	**59.106**	**65.783**	**113.219**	**NA**	**55.945**	**53.981**
	95% CI for GMT	(43.44, 58.86)	(42.00, 66.97)	(45.64, 76.55)	(52.67, 82.17)	(NE, NE)	NA	(39.97, 78.31)	(40.23, 72.44)
	Min, Max	20.00, 5440.37	20.00, 2061.91	20.00, 1961.43	20.00, 1634.36	113.22, 113.22	NA	20.00, 1949.54	20.00, 3178.41
Day 28 post the second dose	N	202	112	94	141	1	NA	71	82
	GMT	**105.373**	**177.862**	**199.164**	**268.381**	**352.541**	**NA**	**206.552**	**212.692**
	95% CI for GMT	(88.67, 125.22)	(145.13, 217.97)	(165.55, 239.60)	(221.71, 324.87)	(NE, NE)	NA	(160.31, 266.13)	(169.59, 266.74)
	Min, Max	20.00, 6863.67	20.00, 2350.68	20.00, 2142.76	20.00, 7725.75	352.54, 352.54	NA	20.00, 2448.99	20.00, 2053.88

Sources: Supplemental Tables IEMT46.1.4.2.a, IEMT46.1.4.2.b, IEMT46.1.4.2.c IEMT46.1.4.2.d, IEMT46.1.4.3.a, IEMT46.1.4.3.c, and IEMT46.1.4.3.d.

The vaccine efficacy has been analysed by similar dose intervals for the SDSD group (Table 22) and whilst the numbers are low the trend seen in vaccine efficacy is consistent with what would be expected based on observed immunogenicity associated with longer dose intervals.

Table 22 Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose by Dose Interval (SDSD Seronegative for Efficacy Analysis Set)

Dose interval	Participants with events, n (%)		VE (%)	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
< 6 weeks	9 / 1702 (0.53)	19 / 1698 (1.12)	53.28	(-3.21, 78.86)	0.060
6–8 weeks	5 / 562 (0.88)	9 / 521 (1.73)	51.08	(-45.57, 83.56)	0.199
9–11 weeks	9 / 1056 (0.85)	24 / 1110 (2.16)	60.55	(15.23, 81.64)	0.017
≥ 12 weeks	4 / 1120 (0.36)	19 / 1126 (1.69)	78.79	(37.63, 92.79)	0.005

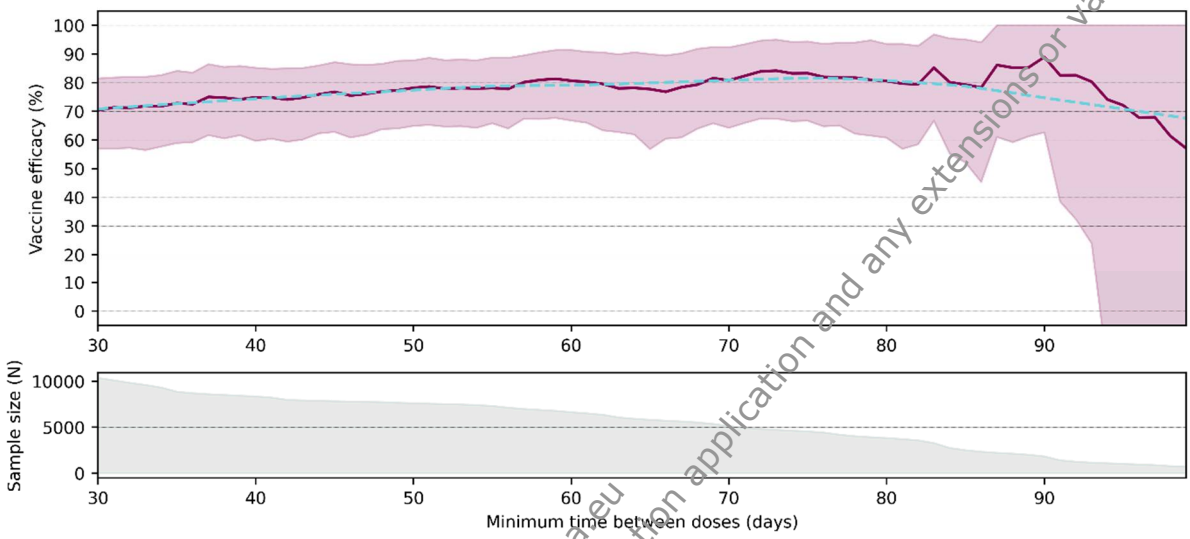
VE of AZD1222 versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.
VE is defined as 1-(incidence of the infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio is derived from 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 endpoints were based on adjudicated events.
Source: Supplemental Table IEMT53.3.1 – 4.

The effect of dose interval on vaccine efficacy has been further explored in the SDSD + LDSD 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 are shown in Figure 9 and Figure 10: 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. The sample sizes become small and the CIs very wide at a dosing interval of approximately 90 days (ie, approximately 12 weeks); therefore, the data cannot be reliably interpreted beyond this point. The minimum dosing interval in these studies was 4 weeks.

Over the dose interval for which there was informative data (up to approx. 90 days), there was a trend towards an increase in efficacy across the dosing interval of 4 to 12 weeks (Figure 9). To substantiate this finding, the analysis was restricted to the SDSD recipients and even after

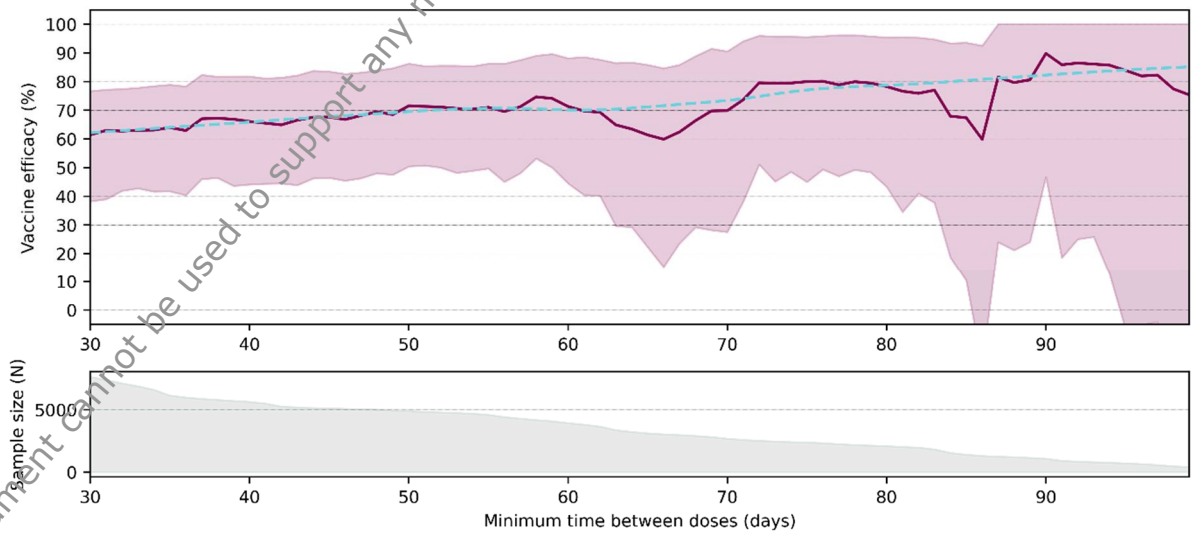
removing the LDSD recipients in whom higher efficacy had been observed, the same trend was demonstrated (Figure 10).

Figure 9 Exploratory Analysis of Median Vaccine Efficacy for Dose Interval (SDSD + LDSD Seronegative for Efficacy Analysis Set



Source: data on file.

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



Source: data on file.

4.2.9.3 Protection after First Dose

An ad hoc analysis was conducted to determine whether protective immunity was induced by the first dose (Table 23). 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 (62.10%, 95.84% CI: 39.96%, 76.08%; Table 8). Over the subsequent 12 weeks Cumulative Incidence plots show divergence, but the amount of data is very limited past this point. 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. Indeed, T cell-mediated responses as measured by IFNγ ELISpot responses peaked after a first dose and may contribute to the protection from symptomatic or severe COVID-19 disease after a single dose (Figure 12).

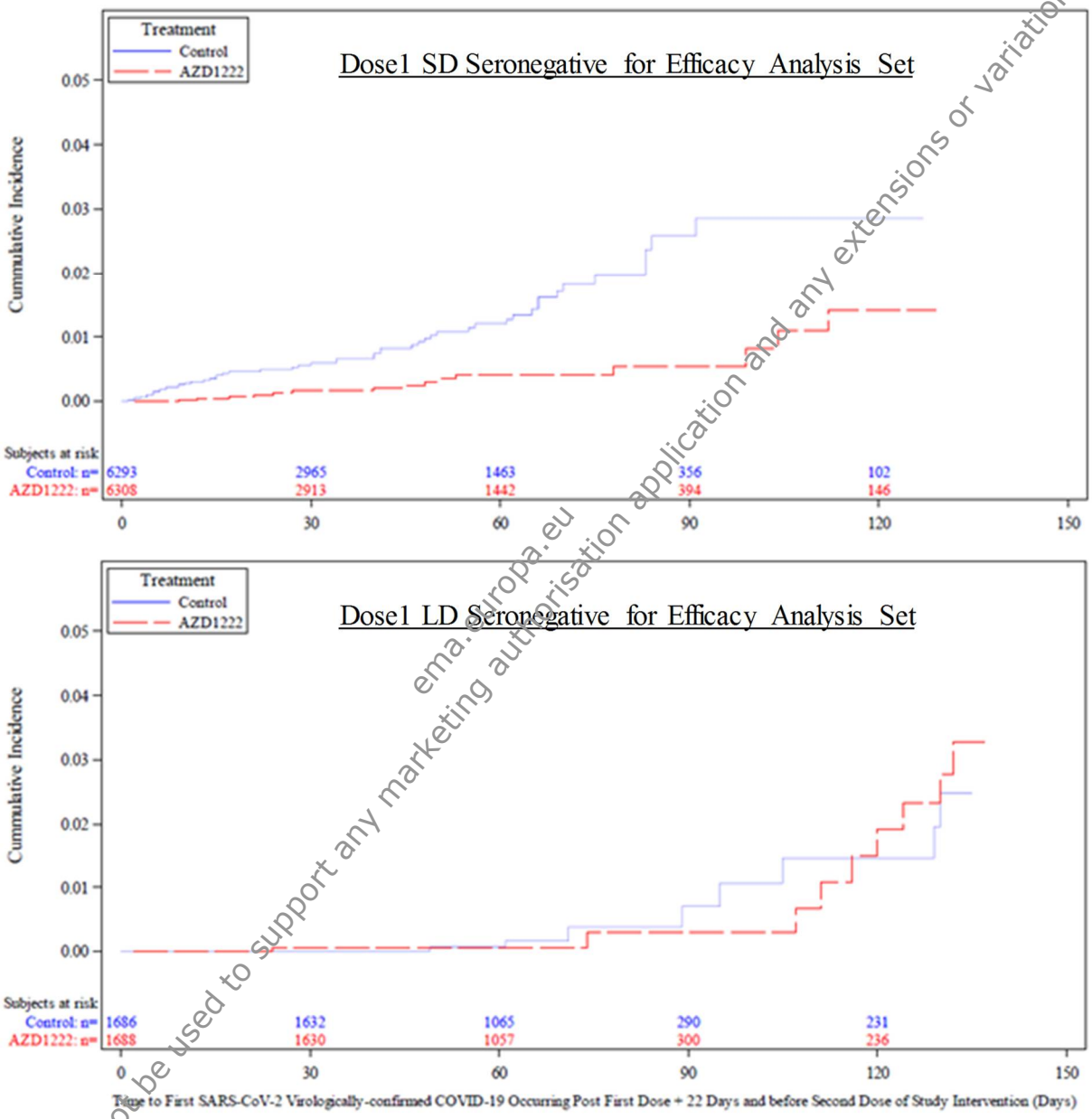
No significant vaccine efficacy was detected after one LD (ie, as the first dose), however the low baseline incidence (8 cases, 0.47%) observed during the follow-up time for 90 days after one LD did not allow a robust evaluation of efficacy during that time frame.

Table 23 Vaccine Efficacy for Incidence of First SARS CoV 2 Virologically confirmed Symptomatic COVID 19 Occurring ≥22 days after dose 1 up to dose 2

	Participants with events						
	AZD1222		Control		VE		
Analysis set [a]	N	n (%)	N	n (%)	(%)	95% CI	P-value
Dose 1 SD	6310	15 (0.24)	6296	52 (0.83)	71.30	(49.02, 83.84)	<0.001
Dose 1 LD	1688	9 (0.53)	1686	8 (0.47)	-12.00	(-189.20, 56.63)	0.815

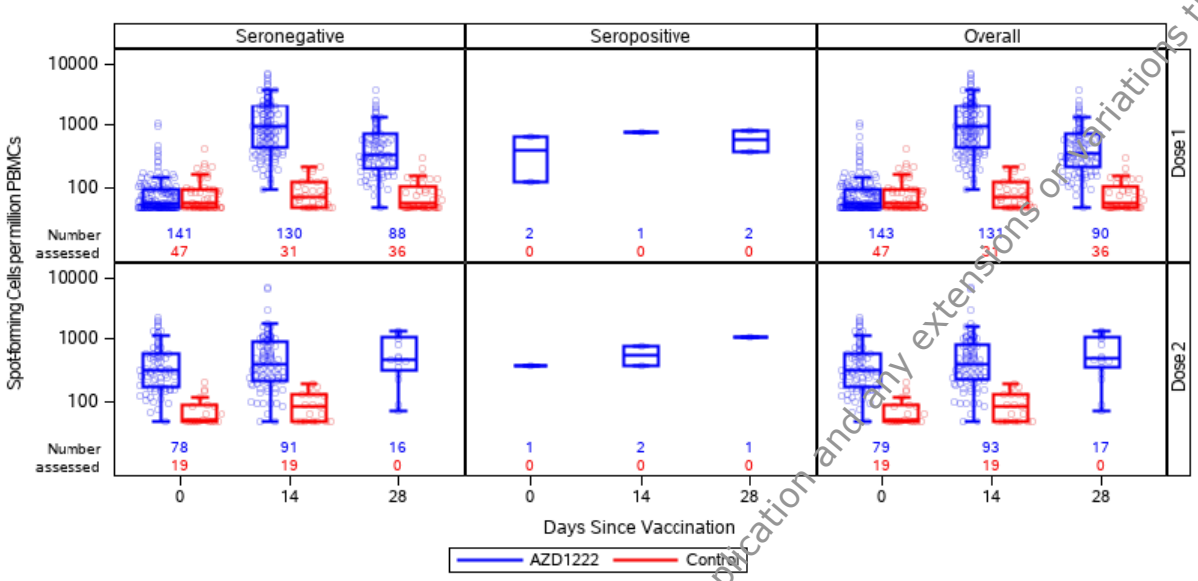
[a] Includes participants who were seronegative at baseline.
VE of AZD1222 versus control, the 95% CI and p-value were estimated based on Poisson regression with robust variance including the terms of study code and age group at screening (18-55 years, 56-69 years, and ≥70 years) as covariates, as well as the log of the follow-up time as an offset.
VE was defined as 1-(incidence of the infection from the AZD1222 arm / incidence of infection 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 IEMT57.1.2 and IEMT57.1.3.

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**



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. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.
COVID-19 endpoints were based on adjudicated events.
Source: Supplemental Figures IEMT59.1 and IEMT59.2.

Figure 12 **IFNy+ Spot Forming Cells Over Time Post Dose 1 and Dose 2 by Serostatus at Baseline**



LLoQ = Lower Limit of Quantification, PBMC=Peripheral Blood Mononuclear Cell, D28 1st Dose = Day 28 post 1st Dose, D28 2nd Dose = Day 28 post 2nd Dose. IFNy spot-forming cells measured as below LLoQ (48) are imputed to a value that is half of the LLoQ. Participants with indeterminate and missing value of baseline serostatus are not included.
Source: Main Immuno Figure 1.7.4.1.1.

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4.3 Efficacy Conclusions

This interim pooled analysis was conducted with 11636 participants in the primary efficacy population with a median follow-up of 19 and 9 weeks after Dose 1 and Dose 2, respectively. It has been demonstrated that a two-dose regimen of AZD1222 was 70.42% (95.84% CI: 54.84%, 80.63%) efficacious against COVID-19. This primary 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 9 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 SDSD regimen, it was shown that 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.

The vaccine was highly immunogenic; after a single dose of SD or LD seroconversion of S-binding antibody was >97% and live neutralising antibody was >80%. After the second dose of SD, this rose to > 99% seroconversion of binding and live neutralising antibody responses. Increasing the dose interval between first and second dose resulted in increases in the binding and neutralizing antibody responses observed. This appears to translate into a trend towards an increase in efficacy across the dosing interval of 4 to 12 weeks.

Adults with pre-existing comorbidity showed similar vaccine efficacy and immune responses to the general population. Older adults (≥ 65 years) experienced too few events to determine vaccine efficacy. Their rates of seroconversion to binding and live neutralising antibody titres were similar to younger adults, but their absolute titres of binding and neutralising antibody tended to be lower. 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 above 65 years of age.

5 OVERVIEW OF SAFETY

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 neutralizing 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 programs 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 adverse events 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 is based on an interim analysis of the pooled results from 4 ongoing University of Oxford-sponsored studies (Study COV001, Study COV002, Study COV003, and Study COV005). 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 6). Unsolicited AEs from the start of each dose through 28 days (ie, day of vaccination and the following 27 days) were also summarized 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 6), and the most extreme result reported in the 28 days post-dose period is presented. Participants were analysed according to actual treatment received.

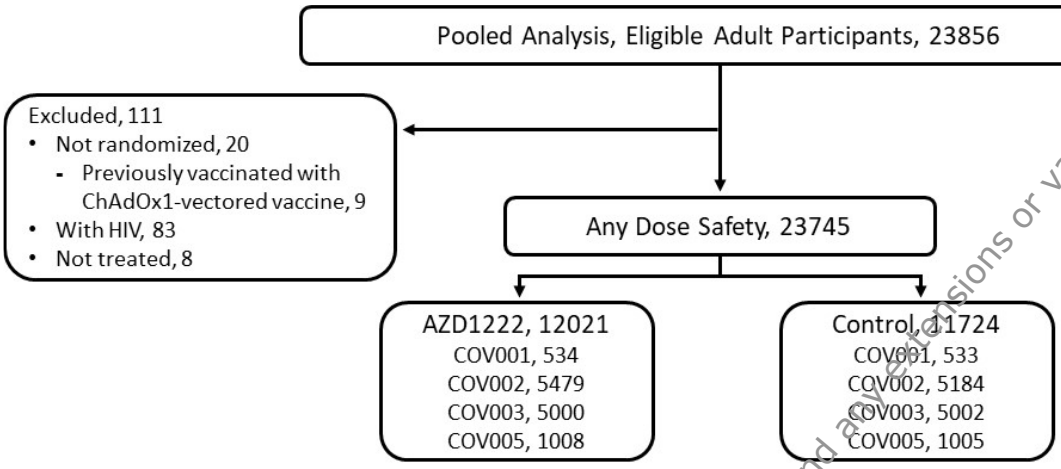
SAEs and AESIs were summarized for all participants throughout the study period (following last vaccination up to the cut-off date). Pre-specified AESIs for AZD1222 were developed in consultation with the US FDA and in line with MHRA guidance and included neurologic, vascular, haematologic, and immunologic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

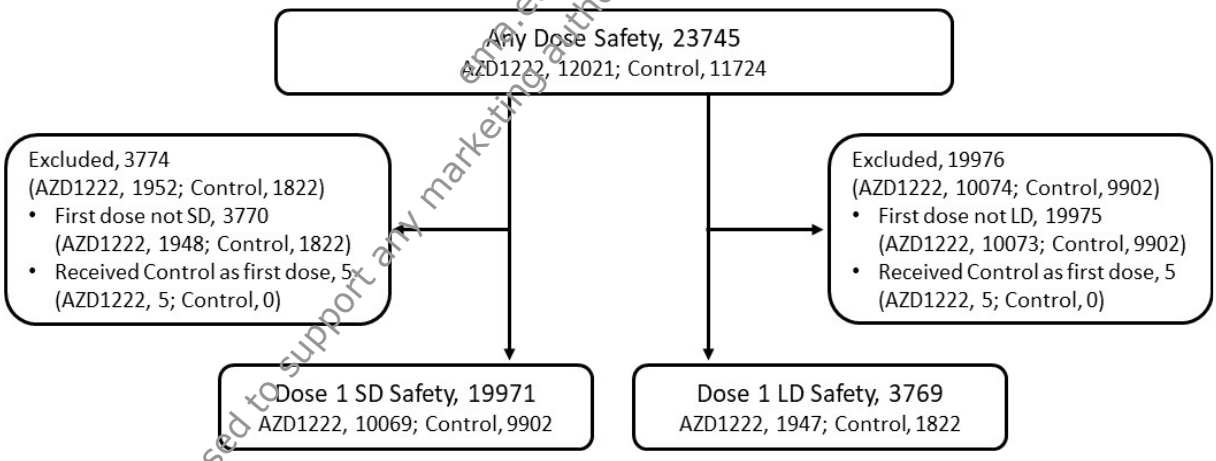
In the Any Dose for Safety Analysis Set, there are a total of 23745 participants who received at least 1 dose of study intervention by the 04 November 2020 cut-off date, including 12021 in the AZD1222 group and 11724 in the control group. The disposition of participants in the pooled analysis sets for safety is provided in Figure 13 and Figure 14.

Figure 13 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.

Figure 14 Participant Disposition, Safety Analysis Sets (AZD1222, Pooled Analysis)



Reasons for exclusion may not be mutually exclusive.
LD = low dose; SD = standard dose.
Source: Main Safety Table 1.1.1.1.

In the Any Dose for Safety Analysis set, the median number of days of exposure was similar between the AZD1222 treatment group (105.0 days) and the control group (104.0 days). The median exposure in the Dose 1 SD Safety analysis set was 90.0 days in the AZD1222 group and 89.0 days in the control group (see Supplemental Table IEMT44).

The two-dose study intervention regimen was received by approximately two-thirds of participants in the AZD1222 group (68.8%) and control group (68.7%) at the time of data cut off. In the AZD1222 group, most participants had received two doses of the SDSD regimen (54.6%) or had only received a single SD before the data cut-off (28.7%) (Table 7). Overall, approximately one-third of participants each had a dose interval in the range of < 6 weeks, 6 to 11 weeks, or ≥ 12 weeks.

Most of the participants were ages 18 to 64 (91.1%), with 8.9% of participants age 65 or older. Overall, in the safety population, 55.8% were female, 44.1% were male, 75.7% were White, 10.2% were Black, 4.1% were mixed race, 3.4% were Asian, and 6.5% were reported to be of other races (see Main Safety Table 1.1.3.1). Most participants (95.1%) were seronegative at baseline (see Main Safety Table 1.1.4.1). Approximately one-third of participants 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, 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 COV003; 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, 2648 participants in the AZD1222 group and 2497 participants in the control group were evaluated for solicited AEs within 7 days after any dose. Solicited local injection site and systemic AEs were reported by 74.7% and 73.0% of evaluated participants, respectively, within the first 7 days following any dose of AZD1222. In the control group, solicited local injection site and systemic AEs were reported by 50.4% and 59.6% of participants, respectively (Table 24). The lower incidence of solicited AEs in the control group is expected given that participants in this group could have received either the MenACWY active control or saline placebo.

Frequencies of individual solicited local and systemic AE terms are provided in (see) Main Safety Tables 1.5.1.2.2 and 1.5.1.3.2. The most frequently reported solicited local injection site AEs within 7 days after any dose of AZD1222 were tenderness (63.7% vs 39.5% in control) and pain (54.2% vs 36.7% in control); other solicited local injection site AEs reported in ≥ 10% of AZD1222 participants were warmth (17.7% vs 14.5% in control), redness (14.0% vs 8.8% in control), itch (12.7% vs 7.5% in control), and swelling (10.0% vs 5.8% in control) (see Main Safety Table 1.5.1.2.2). The most frequently reported solicited systemic AEs within 7 days after any dose of AZD1222 were fatigue (53.1% vs 38.2% in control) and headache (52.6% vs 39.0% in control); other frequently reported systemic solicited AEs were muscle pain (44.0% vs 21.6% in control), malaise (44.2% vs 20.2% in control), feverishness, (33.6% vs 10.7% in control), chills (31.9% vs 8.3% in control), joint pain (26.4% vs 12.4% in control) nausea (21.9% vs 13.1% in control), and fever (7.9% vs 1.2% in control) (see Main Safety Table 1.5.1.3.2).

Most of the solicited AEs following AZD1222 were mild to moderate in severity. A single Grade 4 event was reported after the first dose in the AZD1222 group for fever (ie, > 40˚C). Solicited AEs were generally milder and reported less frequently after the second dose of AZD1222 than after first dose of AZD1222.

During the 7 days following vaccination, the reactogenicity of AZD1222 was highest on Day 1; solicited local injection site and systemic events were reported by 64.7% and 60.8% of participants, respectively, on Day 1 following any dose of AZD1222 (see Safety Tables 1.5.1.4.2 and 1.5.1.5.2). The incidence of participants reporting individual solicited local injection site and systemic AEs decreased to ≤ 2% for most of the individual events by Day 5 to 7, indicating that these events were self-limiting and of short duration. The majority of the events reported on Day 7 were mild or moderate in severity.

By dose interval, the reactogenicity of AZD1222 was lower in participants in the < 6 weeks dosing interval compared with participants in the > 6 weeks dosing intervals. The incidences

of solicited local injection site and systemic AEs following the second dose in the < 6 weeks interval were 38.0% and 36.7%, respectively. For the > 6 weeks dosing intervals, the incidence of solicited AEs ranged from 58.3% to 74.3% for local injection site AEs and 49.2% to 67.1% for systemic AEs. In the control group, similar results were observed, with increased reactogenicity in the dosing intervals > 6 weeks compared with the < 6 weeks dosing interval. No safety concerns were identified for AZD1222 based on the differences observed across dose intervals (see Supplemental Tables IEMT54.1.2, IEMT54.2.2, and IEMT54.3.2).

Generally, a modest attenuation of solicited symptoms was observed in participants that received LD as their first dose in comparison with those that received SD as their first dose (see Main Safety Tables 1.5.1.2.3 and 1.5.1.3.3).

Table 24 Overall Summary of Solicited Adverse Events Collected Within 7 Days After Dose: Pooled Analysis (Dose 1 SD for Safety Analysis Set)

	Days 0 to 7 After Any Dose		Days 0 to 7 After First Dose		Days 0 to 7 After Second Dose	
	AZD1222 (N = 10069)	Control (N = 9902)	AZD1222 (N = 10069)	Control (N = 9902)	AZD1222 (N = 10069)	Control (N = 9902)
Evaluated for solicited AEs, n	2648	2497	2580	2425	1662	1526
Any solicited AE, n (%)	2277 (86.0)	1791 (71.7)	2161 (83.8)	1637 (67.5)	1026 (61.7)	722 (47.3)
Any solicited local AE, n (%)	1979 (74.7)	1258 (50.4)	1839 (71.3)	1117 (46.1)	778 (46.8)	456 (29.9)
Any ≥ Grade 3 severity solicited local AE, n (%)	252 (9.5)	138 (5.5)	210 (8.1)	112 (4.6)	70 (4.2)	38 (2.5)
Any solicited systemic AE, n (%)	1932 (73.0)	1488 (59.6)	1817 (70.4)	1320 (54.4)	741 (44.6)	545 (35.7)
Any ≥ Grade 3 severity solicited systemic AE, n (%)	221 (8.3)	63 (2.5)	192 (7.4)	41 (1.7)	37 (2.2)	27 (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 from Day 0 to Day 6 for COV005 and to Day 7 for rest of studies vis e-diary or diary card.

No grade 4 severity option for events collected in COV005. Pain and Warmth, Malaise, Nausea and Vomiting were not assessed for COV005. Induration, feverishness, and chills did not include COV005 since no severity grading was collected. For Redness, Swelling and Fever severity grading was derived based on reported value. Bruising only collected for COV005.

AE = adverse event; SD = standard dose

Source: Main Safety Table 1.5.1.1.2.

5.4.1.2 Unsolicited Adverse Events

In the Any Dose for Safety Analysis Set, 37.8% of participants in the AZD1222 group and 27.9% of participants in the control group reported an unsolicited AE within 28 days following any dose. A majority of the unsolicited events was mild to moderate in severity, the incidence of events with ≥ Grade 3 severity was 1.9% of participants in the AZD1222 group and 1.5% of participants in the control group (see Main Safety Table 1.5.2.1.1).

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 25). 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. There were no notable imbalances observed for PTs not commonly associated with vaccination. The most frequently reported unsolicited AEs predominantly occurred within ≤ 7 days of any dose; there were no AEs with an incidence ≥ 2% reported after 7 days of any dose (see Main Safety Tables 1.5.2.8.2 and 1.5.2.13.2). Unsolicited AEs with an incidence < 2% reported after 7 days after any dose are provided in (see) Main Safety Table 1.5.2.12.2.

Table 25 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 = 10 069)	Control (N = 9 902)
Vaccination site pain	1197 (11.9)	733 (7.4)
Headache	1051 (10.4)	685 (6.9)
Pyrexia	852 (8.5)	210 (2.1)
Myalgia	852 (8.5)	345 (3.5)
Fatigue	487 (4.8)	290 (2.9)
Chills	392 (3.9)	100 (1.0)
Asthenia	262 (2.6)	123 (1.2)
Malaise	243 (2.4)	138 (1.4)
Nausea	211 (2.1)	117 (1.2)

[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.

AE = adverse event; AESI = adverse event of special interest; PT = preferred term; SAE = serious adverse event; SD = standard dose.

Source: Main Safety Table 1.5.2.3.2.

5.4.2 Serious Adverse Events

In the Any Dose for Safety Analysis Set, fewer than 1% of participants reported an SAE (0.7% of participants in the AZD1222 group and 0.8% of participants in the control group) (see Main Safety Table 1.5.3.1.1). Few participants (5 subjects) reported an SAE that was considered related to study intervention by the investigator (see Main Safety Table 1.5.3.2.1). The following related SAEs (PTs) were reported in the AZD1222 group: pyrexia, C-reactive protein increased, and myelitis transverse. Autoimmune haemolytic anaemia and myelitis were reported as related SAEs in the control group. After the cut-off date, causality for the SAE of C-reactive protein increased was updated by the investigator to not treatment related.

No notable imbalances in the incidence of SAEs by SOC or PT were observed. The most frequently reported SAEs by SOC in the AZD1222 and control groups were infections and infestations (0.1% [18 participants] in the AZD1222 group and 0.2% [27 participants] in the control group) and Injury, poisoning and procedural complications (< 0.1% [10 participants] in the AZD1222 group and 0.1% [13 participants] in the control group). There were no

clinical meaningful imbalances in the incidence of SAEs by SOC or PT between the AZD1222 and control groups (see Main Safety Table 1.5.3.1.1). Three cases of potential immune-mediated neurological conditions were reported as SAEs; these events were also determined to be AESIs and are therefore discussed in Section 5.4.3.

A total of 6 SAEs with a fatal outcome (2 in the AZD1222 group and 4 in the control group) occurred as of the cut-off date (see Main Safety Table 1.5.3.5.1). One of the deaths in the AZD1222 group occurred after the cut-off date (PT: neoplasm malignant); the other death in the AZD1222 group was due to a PT of Fungal pneumonia. The 4 deaths in the control group were due to PTs of COVID-19 pneumonia, craniocerebral injury, injury, and homicide. 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 (0.8% of participants in the AZD1222 group and 1.1% 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 events and potential immune mediated neurologic conditions, the most frequently reported PTs (≥ 5 participants in the AZD1222 group) were paraesthesia (0.3% [37 participants] in the AZD1222 group vs 0.4% [48 participants] in the control group), hypoaesthesia (0.1% [13 participants] in the AZD1222 group vs 0.2% [19 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). Nonserious AEs of facial paralysis occurred in 3 participants in the AZD1222 group and 3 participants in the control group. In the control group, one participant reported a nonserious event of perineal paraesthesia which the investigator considered to be a potential acute sensory polyradiculopathy.

Three cases of potential immune-mediated neurological conditions were reported as SAEs; 2 (< 0.1%) in the AZD1222 group and 1 (<0.1%) in the control group (see Main Safety Table 1.5.3.1.1). 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. More detailed case descriptions are provided below. See Safety Narratives, Module 5.3.5.3 for narratives for these events.

The event of PPD in the PPD group occurred in a <=60-year-old female PPD

The event of PPD in the PPD group occurred in a <=60 year-old female PPD

The event of PPD in the PPD PPD occurred in a <=60 year-old male who PPD

Immunologic Reactions

In the AZD1222 group, a non-serious event of anaphylactic reaction was reported 63 days after vaccination (data on file). It occurred during an episode of tonsillitis treated with antibiotics. The participant presented with rash and shortness of breath and was treated with IM adrenaline and chlorphenamine. There was no hypotension or airway issues and no rise in mast cell tryptase.

One event of angioedema was reported 8 days after vaccination in the AZD1222 group. While not included as a pre-specified AESI, angioedema may be of clinical interest. The event of angioedema was nonserious and occurred after crab ingestion (data on file).

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 (12 participants [0.1%]) compared with the control group (23 participants [0.2%]) (Main Safety Table 1.5.4.1). Two participants in the AZD1222 group had SAEs of COVID-19, compared with 13 participants in the control group who had serious events of COVID-19 or COVID-19 pneumonia (see Main Safety Table 1.5.3.1.1).

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). 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. However, there were no AEs of leukopenia, thrombocytopenia, or neutropenia reported for the AZD1222 group (see Main Safety Table 1.5.2.2.1). The incidence of Grade ≥ 3 biochemistry parameters was balanced between groups.

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 (35.7% in the AZD1222 group and 36.0% in the control group) had a comorbidity at baseline. The most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%). 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, and 2.1.4.1.b).

AZD1222 was well tolerated in both 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).

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 (Comorbidity Safety Tables 2.5.2.1.1.a, 2.5.2.1.1.b, 2.5.2.2.2.a, 2.5.2.2.2b, 2.5.3.5.1a, 2.5.3.1.1.b, 2.5.3.1.1.b, 2.5.4.1.a, and 2.5.4.1.b).

Laboratory results were consistent by comorbidity subgroup (see Comorbidity Safety Tables 2.6.1.1.a, 2.6.1.1.b, 2.6.2.1.a, and 2.6.2.1.b).

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

5.4.5.2 Older Adults

Overall, 8.9% of participants were in the ≥ 65 years of age subgroup, and 6.1% 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 aged 18-64, 73.9% were White; among those aged 65 and above, 93.6% were White (see Age Safety Tables 4.1.3.1.a, 4.1.3.1.b, 2.1.4.1.a, and 2.1.4.1.b).

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 dose than after the first dose 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).

The incidence of unsolicited AEs reported within 28 days of any AZD1222 dose was also lower in the in older adults ≥ 65 years of age (25.1%) compared to younger adults 18 to 64 years of age (41.8%). 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 dose was low in both the older adults (1.1%) and younger adults 18 to 64 years of age (2.0%) subgroups (see Age Safety Tables 4.5.2.1.1.a and 4.5.2.1.1.b).

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 0.6% (68 participants) in the AZD1222 group and 0.8% (86 participants in the control group. In the ≥ 65 years of age, SAEs were reported by 0.5% (11 participants) in the AZD1222 group and 0.3% (3 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).

Laboratory results were consistent by age group (see Age Safety Tables 4.6.1.1.a, 4.6.1.1.b, 4.6.2.1.a, and 4.6.2.1.b).

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. 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).

Overall, there was no clinically meaningful imbalance in the reactogenicity profile of AZD1222 across countries; there was no notable imbalance 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).

Although not clinically meaningful, there was a difference in the incidence of unsolicited AEs reported in the AZD1222 group observed in in Brazil (52.5%), with a tendency towards higher incidences of AEs compared with the UK (28.0%) and South Africa (26.9%) (see Country Safety Tables 3.5.2.1.1.a, Table 3.5.2.1.1.b, Table 3.5.2.1.1.c, 3.5.2.2.1.a, 3.5.2.2.1b, and 3.5.2.2.1.c).

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).

Laboratory results observed by country were consistent with the overall population (see Country Safety Tables 3.6.1.1.a, 3.6.1.1.b, 3.6.1.1.c, 3.6.2.1.a, 3.6.2.1.b, and 3.6.2.1c).

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

5.4.5.4 Serostatus

Overall, most participants (95.1%) in the Any Dose for Safety Analysis Set were seronegative at baseline (see Main Safety Table 1.1.4.1). 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). For the AZD1222 group, seronegative participants were predominantly White (77.2%), while seropositive participants were White or Black (43.0% and 44.6%, respectively). Based on the limited data in participants who were seropositive (345 participants in the AZD1222 group and 373 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 5.5.1.1.2.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, and 5.5.1.3.2.b). 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, 5.5.2.2.2.a, and 5.5.2.2.2b). The was no evidence of a change in severity by serostatus for unsolicited AEs, which were reported in 2.1% of participants who were seronegative at baseline and 1.2% of participants who were seropositive at baseline in the AZD1222 group (see Serostatus Safety Tables 5.5.2.1.2.a and 5.5.2.1.2.b).

There were no clinically meaningful imbalances in the incidence of SAEs or AESIs between the AZD1222 and control groups by serostatus (see Serostatus Safety Tables 5.5.3.1.1.a, 5.5.3.1.1.b, 5.5.4.1.a, and 5.5.4.1.b).

Laboratory results observed by country were consistent with the overall population (see Serostatus Safety Tables 5.6.1.1.a, 5.6.1.1.b, 5.6.2.1.a, and 5.6.2.1.b).

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 concern.

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 paracetamol to be administered before vaccination and participants were advised to continue with 1 gram of paracetamol every 6 hours for 24 hours to reduce vaccine-associated reactions. All participants within this subset were randomised equally to the vaccine or control arms of the study. To assess the effect of prophylactic paracetamol use, the occurrence of adverse reactions in the first 2 days after vaccination was analysed.

A total of 56 participants in the AZD1222 group and 57 in the control group received prophylactic paracetamol (Table 26). The incidences of pain, feverishness, chills, muscle pain, headache, and malaise were numerically lower among participants in the AZD1222 group that received prophylactic paracetamol compared with participants that did not receive prophylactic paracetamol. Similar reductions in AE incidences were also observed in participants in the control group when comparing paracetamol and no 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, the use of prophylactic paracetamol may reduce reactogenicity in participants receiving AZD1222.

Table 26 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	320 (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)
Feverishness	22 (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.

5.5 Post-marketing Safety Reports

Not applicable; AZD1222 is not marketed in any region or country.

5.6 Safety Conclusions: Safety Profile of AZD1222

This interim pooled analysis was conducted with 23745 participants in the Any Dose for Safety Analysis, including 12021 who received at least 1 dose of AZD1222, and 11723 who received at least 1 dose of control, with a median follow-up of 105 days in the AZD1222 group and 104 days in the control group.

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 headache, nausea, muscle pain, joint pain, fatigue, malaise, feverishness, chills, fever and local injection site reactions (tenderness, pain, warmth, redness, itch, swelling). Unsolicited AEs were consistent with AEs commonly observed following vaccination. There were no notable imbalances observed for PTs not commonly associated with vaccination.

The incidence of SAEs was low (< 1%) in both the AZD1222 and control groups, with no difference in either frequency or type of SAEs between the treatment groups. A total of 6 SAEs with a fatal outcome (2 in the AZD1222 group and 4 in the control group) occurred as of the cut-off date. None of these events were considered related to study intervention by the investigator.

Few AESIs were reported (0.8% of participants in the AZD1222 group and 1.1% 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 events and potential immune-mediated neurologic conditions, the most frequently reported PTs were paresthesia, hypoaesthesia, and muscular weakness. The incidence of these 3 PTs was numerically lower in the AZD1222 group than in the control group. Nonserious AEs of facial paralysis occurred in 3 participants in the AZD1222 group and 3 participants in the control group. There were 3 SAEs of demyelinating events; 2 cases in the AZD1222 group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group. There was no evidence of an association between AZD1222 and PTs related to possible VAED, which were reported by a slightly lower percentage of participants in the AZD1222 group.

There were no clinically relevant differences in the safety profile by comorbidity, country, 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

The indication being sought for the AZD1222 vaccine is active immunisation of adults aged from 18 years for the prevention of COVID-19. The recommended vaccination regimen is 2 standard doses with an interval of 4 to 12 weeks between. The benefits and risks of AZD1222 for the proposed indication with the recommended vaccination regimen are evaluated below.

6.1 Benefits of AZD1222

The evaluation of the efficacy of AZD1222 for prevention of COVID-19 is based on the pooled data from 2 ongoing clinical studies up to a cut-off date of 04 November 2020, comprising adults aged from 18 up to PPD years. There was good representation of persons at high risk of severe outcomes of COVID-19, namely the older adults (9% were ≥ 65 years) and those with pre-existing disease(s) or obesity, where 36% had at least one of cardiovascular disease, respiratory disease, diabetes or obesity (BMI ≥ 30 kg/m^2). However, individuals with severe or uncontrolled disease were excluded from the clinical studies.

The primary efficacy analysis demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 70.42% (95.84% CI: 54.84%, 80.63%) from 15 days after the second dose in seronegative participants receiving two doses (SDSD or LDSD). The primary analysis was supported by sensitivity analyses restricted to participants who received two SD (SDSD) and participants in the ITT analysis set, both showing consistent vaccine efficacy. Moreover, protection against COVID-19 was induced already after the first SD, as shown in an exploratory analysis from 22 days after the first SD up to the second dose/after one SD (vaccine efficacy = 71.30%, 95% CI: 49.02%, 83.84%). This was also supported by an induced immune response observed at 28 days after the first SD.

Secondly, data consistently demonstrated that AZD1222 provides protection against COVID-19 hospitalisations. No hospitalisations occurred in the AZD1222 group (0/5807) compared to 5 cases in the control group (5/5829) from 15 days after the second dose (SDSD or LDSD) in seronegative participants. Similarly, no COVID-19 hospitalisations occurred in the AZD1222 group (0/6307) receiving SD as first dose compared to 9 in the control group (9/6297) from 22 days after the first dose in seronegative participants (vaccine efficacy = 100%, 97.5% CI: 49.55%, NE; p = 0.004).

Further, the vaccine efficacy of AZD1222 was similar in participants with at least one comorbidity (vaccine efficacy = 73.43%, 95% CI: 48.49%, 86.29%), as compared with the overall population from 15 days after the second dose (SDSD or 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.

The number of older adults (≥ 65 years) with available data was too small to determine vaccine efficacy. In this subgroup, the rates of seroconversion to binding and live neutralising antibody titres were similar to younger adults, but their absolute titres of binding and neutralising antibody tended to be lower. However, the titres for S-binding antibodies observed in the older adults were similar to the titres in Brazilian participants for whom the vaccine efficacy was demonstrated.

The interim pooled analysis is based on limited duration of follow-up to assess the duration of protection by AZD1222 against COVID-19, but protection over longer follow-up time will be evaluated as more data from the ongoing studies accrue.

Finally, an important factor determining the degree to which a vaccine is able to positively impact the course of the global COVID-19 pandemic is wide access to the vaccine. The AZD1222 formulation is to be stored at 2°C to 8°C, meaning it can be easily distributed and stored in a normal refrigerator for several months, which may facilitate access in healthcare settings, including care homes and pharmacies.

6.2 Risks of AZD1222

The evaluation of the safety of AZD1222 is based on the pooled population from 4 ongoing studies, comprising 23745 male and female adults aged from 18 years to PPD years, who received at least one dose of study drug (12021 received AZD1222 and 11724 received control) up to the data cut-off date 04 November 2020. A majority (> 68%) of participants had received 2 doses, and most participants (55%) in the AZD1222 group had received 2 standard doses, which is the recommended dosing regimen. The median exposure time was similar in the AZD1222 (105.0 days) and the control groups (104.0 days).

Overall, vaccination with AZD1222 was well tolerated. The incidence of SAEs was low (< 1%) in both the AZD1222 and control groups, with no difference in either frequency or type of SAEs between the treatment groups. There were 6 SAEs with a fatal outcome (2 in the AZD1222 group and 4 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 headache, nausea, muscle pain, joint pain, fatigue, malaise, feverishness, chills, 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. For other types of AEs not commonly associated with vaccination, there were no notable imbalances between AZD1222 and control. Further, there were no reported acute allergic reactions with AZD1222 administration.

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; 2 cases in the AZD1222 group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group, with all cases occurring in study COV002. 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 there is a theoretical concern that vaccination 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 (0.2%), thus, 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.

A limitation in the current safety evaluation of AZD1222 is the limited duration of follow-up, however, long-term follow-up of the ongoing clinical studies will provide data to further characterise the safety profile of AZD1222. Moreover, since persons with severe immunodeficiency, severe underlying 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

The novel AZD1222 vaccine was confirmed with a clinically meaningful benefit of effective protection against symptomatic COVID-19. The potential of AZD1222 was reinforced by the fact that no severe cases of COVID-19, and no COVID-19 hospitalisations after 10 days post first dose, were reported in participants receiving AZD1222, thus highlighting an important advantage not only for the health of the vaccinees but also in reducing utilization of healthcare resources. Overall, vaccination with AZD1222 has the potential to be a critical intervention both for the individual and for public health, in preventing COVID-19 and its associated risk of severe morbidity and mortality.

Given that older people and those with preexisting disease are at higher risk of severe COVID-19 outcomes, the unmet medical need is generally greatest in these groups of the population. In this light, the results showing a consistently effective protection against COVID-19 both in participants with or without background comorbidities are reassuring. Older adults (≥ 65 years) experienced too few events to determine vaccine efficacy, but trends were in line with those in the general population. The humoral antibody response in older

adults tended to be lower than younger adults, but the clinical significance of this observation is currently unknown. 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. However, persons with severe diseases were excluded from the clinical studies, and therefore, the benefit-risk profile in these individuals has not been confirmed.

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, including a population-based analysis of nearly 64 million vaccine doses in the US, concluding that if there is any association between TM 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 MS, 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 (Principi and Esposito 2020, Mouchet et al 2018, Phillips et al 2018). 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, this is a theoretical risk in relation to AZD1222 vaccination, as there were no data suggesting an association between AZD1222 and VAED and therefore, 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 effective and safe vaccines are needed. With its proven effect in preventing COVID-19 and related hospitalisations, together with a favourable safety profile, AZD1222 is anticipated 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 is favourable for the proposed indication in adults from 18 years, including older adults from 65 years and those with comorbidities. Thus, AZD1222 is anticipated to have a significant impact both for individuals and public health in the ongoing COVID-19 pandemic crisis.

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8 LIST OF APPENDICES

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

Appendix B Justification for Missing Studies

SIGNATURE PAGE

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Low Dose Delivery in Study COV002 and COV005

Drug Substance	AZD1222
Date	18 December 2020

Low Dose Delivery of AZD1222 in Study COV002 and Study COV005

AZD1222-Prevention of COVID-19

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this Clinical Summary.

Abbreviation or special term	Explanation
AEX	Anion exchange chromatography
ARV	Anti-viral therapy
CBF	Clinical biomanufacturing facility
COVID-19	Coronavirus disease 2019
ChAdOx1 nCoV-19	Name of AZD1222 when initially developed by the University of Oxford
dd PCR	Digital droplet polymerase chain reaction
DP	Drug product
FFF-MALS	Field flow fractionation multi-angle light scattering
GC	Genome copy
HIV	Human immunodeficiency virus
ifu	Infectious particle per dose
IM	Intramuscular
LD	Low dose
MenACWY	Meningococcal Group A, C, W-135 and Y conjugate vaccine
MHRA	Medicines and healthcare products regulatory agency
NT	Not tested
NTA	Nanoparticle tracking analysis
qPCR	Quantitative polymerase chain reaction
P:I	Viral particles : Infectious particle
PS80	Polysorbate 80
SD	Standard dose
SA	South Africa
s.f	Significant figure
SGS	Contract laboratory
SOP	Standard operating protocol
vg	Viral genome
vp	Viral particles

1 INTRODUCTION

The clinical development programme investigating the efficacy, safety, and immunogenicity of AZD1222, previously referred to as ChAdOx1 nCoV-19 vaccine, for the prevention of COVID-19 consists of 8 ongoing studies, including 5 University of Oxford-sponsored studies and 3 AstraZeneca (AZ)-sponsored studies. Development of AZD1222 was initiated by the University of Oxford with subsequent transfer of development activities to AZ. Several batches of AZD1222 have been produced for these clinical trials using 3 processes (Processes 1-3) by Oxford University in the UK (Process 1), Advent in Italy (Process 2) and by COBRA/Symbiosis in the UK (Process 3).

This document summarises how the low dose (LD) and standard dose (SD) administration of AZD1222 occurred during the ongoing COV002 and COV005 studies. COV002 is a Phase 2/3, participant-blinded individually randomised controlled trial sponsored by University of Oxford (Oxford), administering either a single dose or 2-doses of AZD1222 or licensed MenACWY vaccine via intramuscular (IM) injection. COV005 is an ongoing, phase1/2, double-blinded study in South Africa (SA) in healthy adults aged 18 to 65 years living without HIV.

2 MANUFACTURING PRODUCT HISTORY OF AZD1222

The Drug Product (DP) manufacturing process for AZD1222 comprised of the pooling, dilution and mixing, bioburden reduction filtration, sterile filtration, aseptic filling, and finish of the DP.

The manufacturing processes were developed as follows:

- Process 1 was the clinical process that was developed to produce a frozen liquid DP (0.35 mL or 0.485 mL in 2R vial) manufactured by Oxford's Clinical Biomanufacturing Facility (CBF), UK. Process 1 material was used in the Oxford University sponsored Phase 1 clinical study, COV001.
- Process 2 was the clinical process that was developed to produce a frozen liquid DP (1.2 mL in 3 mL vial) manufactured by Advent S.R.L. (Italy). Process 2 material was used in the Oxford University sponsored Phase 1 clinical study, COV001 and Phase 2/3 clinical studies: COV002, COV003, COV004, and COV005.
- Process 3 was the clinical process that was developed to produce a liquid DP (5 mL in 10R vial) manufactured by Cobra, filled at Symbiosis Pharmaceutical Services (UK); and tested by SGS for Abs260, and by Advent for qPCR and infectivity. Process 3 material was used in the Oxford University sponsored Phase 1/2 clinical study, COV001, and in Phase 2/3 clinical studies: COV002, COV003, COV004, and COV005. This was also used in AZ sponsored Phase 3 clinical study D8110C00001 in the US and other regions, and in Phase 2/3 study D8111C00002 in Japan.

3 AZD1222 CLINICAL STUDIES

A Phase 1/2 clinical trial COV001 initiated on 23 April 23 2020, was followed by 3 randomised controlled trials of the AZD1222 in the UK (COV002), Brazil (COV003), and SA (COV005). Of these studies only COV005 is a double blind study, the other 3 being single-blind. All studies include monitoring of COVID-19 occurrence to support efficacy analyses. The enrolment of their respective efficacy cohorts has been completed and the studies are currently in the follow-up phase. Studies COV001, COV002, COV003, and COV005 were initially designed to assess a single-dose of AZD1222 compared with control, however after a review of immunogenicity data from COV001, a booster dose was incorporated in the dosing schedule of the other studies.

This document describes the LD delivery in COV002 and COV005 as a result of variability in the AZD1222 (DP release assays. The strength of the AZD1222 dose is expressed in 2 different units, viral particle/mL (vp/mL) and viral genome/mL (vg/mL) that are equivalent, and used interchangeably in the document. The different units reflect the assay used to assess the strength, with viral particle concentration being determined by spectroscopic method and the viral genome concentration determined by qPCR. It is important to note that while the interpretation of release assays early in the programme led to LD administration in some subjects, it is now well understood and controlled, leading to consistent and robust strength determination.

3.1 Study COV002

Study COV002 is an ongoing Phase 2/3, single-blind, individually randomised, active-controlled study in adults and healthy children in the UK, administering either a single dose or 2 doses of AZD1222 or licensed MenACWY vaccine via IM injection. The study aims to assess efficacy, safety, and immunogenicity AZD1222.

Participants were enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focused on health care professionals and other adults with high potential for exposure to COVID-19. The study is comprised of 12 main study groups (Groups 1-12), with an overall sample size of up to 12390 participants. Of these, Groups 4, 6, 9, and 10 are the main groups for evaluating efficacy in each age group. Participants are randomised to AZD1222 or MenACWY (control) by group, and all participants are blinded to the allocation of the study intervention groups.

The intended AZD1222 dosing regimens to be evaluated for efficacy was a SD/SD 2-dose regimen. However, due to a difference in concentration determination between 2 analytical methods, some participants received a lower dose of approximately 2.2×10^{10} vp instead of the planned dose of 5×10^{10} vp. The study protocol was then amended to group the participants who received this LD/SD regimen separately for efficacy evaluation (Group 4).

The study sample size was expanded and participants newly enrolled into another group receiving the intended SD/SD regimen (Group 6). A small number of participants from Groups 1, 2 and 5a (not part of the primary efficacy cohort) also received a LD.

Table 1 shows the dose administered to the participants from study groups 4, 6, 9, and 10 which are the main groups for evaluating efficacy in each age group. A reduced concentration (LD) was administered as Dose 1 in a 1716 participants in Group 4 from lot # K.0007.

Table 1 Dose Administered in COV0002 Study Groups 4, 6, 9, and 10

Group	Description (Age)	Dose 1	Dose 2
4	18-55	Low dose (A)	Standard dose (A, S)
6	18-55	Standard dose (A)	Standard dose (A, S)
9	56-69	Standard dose (S)	Standard dose (S)
10	+70	Standard dose (S)	Standard dose (S)

Low dose: ≈$2.2x10^{10}$ vp and Standard dose $5.0x10^{10}$ vp

A= Advent S= Symbiosis/Cobra

Low dose was administered to participants from COV002 study (Group 4); in 1716 participants as Dose 1 and in 50 participants as Dose 2 (Table 2). The lot batch numbers of the DP used in the COV002 studies were K.0007, K.0008, and K.0009 from Advent (Process 2) and 20482B from Cobra/Symbiosis (Process 3).

The concentration calculation differences of Lot # K.0007 resulting in administration of the LD in COV002 is described in Section 3.1.1

Table 2 Low Dose Administration in COV002 (Group 4) and COV005 study

Study	# of participants with LD (Dose 1)	Batch #	# of participants with LD (Dose 2)	Batch #
COV002 (Group 4)	1716	K.0007	47	K.0008
			3	K.0009
COV005	21	K.0011	23	K.0011

LD = low dose

3.1.1 Dose volume calculation for Process 2 Drug Product from batch # K.0007 lot resulting in low dose

A quality control analysis of DP used in the COV002 study revealed discrepancies between analytical methods used by CBF and Advent to quantify viral particles, namely spectrophotometry and quantitative PCR (qPCR). On testing of Advent manufactured lot K.0007 an approximately 2.3 fold difference in determined viral particle (vp) content (3.89 ×

10^{11} vp/mL by CBF spectrophotometry, compared to 1.7×10^{11} viral genome (vg)/mL by Advent's quantitative polymerase chain reaction (qPCR) assay was identified.

Due to the large number of variables in the respective manufacturing processes and methods to testing of concentration, neither manufacturer could definitively account for the difference in viral particle content determination. In consultation with the MHRA, it was agreed to dose based on viral particle content as ascertained by the CBF's spectrophotometric method to maintain consistency with the COV001 study and ensure volunteers were not given a higher than planned dose for safety considerations. This resulted in selection of a dose of 5×10^{10} viral particles by spectrophotometer (2.2×10^{10} viral particles by qPCR) from lot K.0007. Administration of the required dose was facilitated using a dilution protocol. Table 3 shows calculation of the required dose volume for lot K.0007 based on the agreed spectrophotometric assay. A diluted version of this lot was then used in a subset of participants in the COV002 study. The intended dose for administration was 5 x 10^{10} vp.

Table 3 Dose Volume Calculation for K.0007

Dose/dilution calculation		Batch: K.0007
Product concentration of original vial	A =	3.89 x 10^{11} vp/mL
To prepare dilution in volume of	B =	4000µL
Dilution ratio required	C =	1/4
Volume of ChAdOx1 nCOV-19 required	D =	1000µL
Volume of 0.9% saline for injection required	E =	3000µL
Concentration following dilution	F =	9.73^{10} vp/mL
Intended dose for administration	G =	5 x 10^{10} vp
Volume to be extracted (G/F) x 1000		500µL (1 s.f)

G= Intended dose for administration, F= concentration following dilution, s.f = significant figure
Source: Oxford Standard operating protocol, COV002 vaccine preparation, V3.0

However, this was revisited after investigators reported observations that vaccinated participants experienced low reactogenicity. The comparative testing of physicochemical and strength related criteria of the AZD1222 DP using the same methods demonstrated that whilst nearly all the physicochemical characteristics were similar across these processes, the Process 2 DP (Advent lot #s K.0007, K.0008, and K.0009) used in the COV002 study had almost twice the concentration of Polysorbate 80 %(w/v). In the case of K.0007, the dosage evaluated in the comparability assessment was SD based on Advent qPCR concentration. During the conduct of the study, the testing method applied by CBF to determine concentration did not account for the effect of the higher concentration of PS80 in the DP. 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 ~ half the intended dose administered to 1716 participants in the study. It was concluded that the actual clinical dose administered was likely to be a LD of 2.2×10^{10} vg for lot K.0007 as determined by the Advent concentration of 1.7×10^{11} vg/mL (which was the value stated on the label). The comparative analyses conducted using the same analytical methods and necessary corrections across DP lots demonstrated that the clinical dosage across all three processes were comparable. On recalculation of the original dose of K.0007 the study dosing was adjusted to switch to the SD. All subsequent lots of Advent's DP for COV002 were tested using the Advent qPCR assay to determine dose concentration.

3.1.2 Dose Volume Calculation for Process 2 Drug Product from batch # K.0008 and K.0009 Lot Resulting in Low Dose

The Vaccine Preparation and Administration Standard Operating Procedure from Oxford included calculations for establishing a high dose (SD) and a LD for K.0008 and K.0009 formulation based on Advent qPCR dose calculation method. The LD was established by halving the volume of injection used for the high dose (Table 4). This LD was administered in a few participants in COV0002 study as Dose 2 (Table 2).

Table 4 Dose preparation for Low Dose in COV002 Study for batch # K.0008 and K.0009 by qPCR Dose Calculation Method

Dose/Dilution Calculation (Low Dose)		Batch: K.0009	Batch: K.0008
Product concentration in original vial	A =	1.4×10^{11} vp/mL	2.1×10^{11} vp/mL
Volume of neat vaccine in vial	B	1.2 mL	1.2 mL
Total dose available in vial (A/1000) x B	C	1.68×10^{11} vp	2.52×10^{11} vp
To prepare dilution in volume of	D	1.65 mL	2.5 mL
Dilution ratio required	E	1.2:0.45	1.2:1.3
Volume of AZD1222 required	F	1.2 mL	1.2 mL
Volume of 0.9% saline for injection required	G	0.45 mL	1.3 mL
Concentration following dilution (C/D) x 1000	H	1.02×10^{11} vp/mL	1.01×10^{11} vp/mL
Intended dose for administration	I	2.2×10^{10} vp	2.2×10^{10} vp

Table 4 Dose preparation for Low Dose in COV002 Study for batch # K.0008 and K.0009 by qPCR Dose Calculation Method

Dose/Dilution Calculation (Low Dose)		Batch: K.0009	Batch: K.0008
Volume to be extracted (G/F) x 1000	J	0.22 mL 2.sf	0.22 mL 2.sf

I= Intended dose for administration, H= concentration following dilution, s.f = significant figure
Source: Oxford Standard operating protocol, COV002 vaccine preparation, V6.0

3.2 Study COV005

COV005 is an ongoing, phase1/2, double-blind study in SA in healthy adults aged 18 to 65 years, initiated on 28 June 28 2020. Two doses of AZD1222 at a dose of 3.5-6.5 × 10^{10} vp, were administered at an interval of 4 weeks. Participants in the control group were administered saline solution. In the COV005 study, 21 and 23 participants received low dose from Lot # K.0011 as Dose 1 and 2 respectively (Table 2, Voysey et al).

3.2.1 Dose volume calculation for Process 2 Drug Product from batch # K.0011 lot resulting in low dose

In the COV005 study, 44 participants were also administered a lower dose of AZD1222 from the DP batch K.0011 from Advent. This was a result of an overestimation of the viral particle content in the DP as measured by qPCR by Advent. Remeasurement of the viral particle content in the DP using commercially optimised qPCR and digital droplet PCR (dd PCR) methods by AstraZeneca yielded values that were lower than that estimated by Advent. The consistency between the results obtained via these 2 different methods used by AstraZeneca provided a more accurate and reliable measure of the viral particle content in the DP. It was concluded that the qPCR viral particle content for K.0011 as ascertained by Advent was artificially high (cause unknown). Due to this initial overestimation of the viral particle content, the first few participants were administered a lower volume of injection to achieve the SD (21 as their first dose and 23 as their second dose) (Voysey 2020). In light of the values obtained during the remeasurement, the dose injection volume was altered to achieve a comparable SD to the other studies after consultation with the South African Regulatory authorities. The revised dosing volume of K.0011 was decided based on the totality of the data available, importantly by taking into consideration the AZ qPCR, AZ ddPCR, and AZ infectivity data to bring the dosage of this lot comparable to the ranges of previous lots for all three measures of the strength (vp/dose, vg/dose, ifu/dose).

4 COMPARABILITY ASSESSMENT OF CLINICAL MANUFACTURING PROCESSES 1, 2, AND 3 BY ASTRAZENECA

The DP lots of AZD1222 from Process 1, 2, and 3 were tested by updated methods by AZ in order to support the clinical comparability assessment using the best available methodology, and to facilitate the subsequent comparability assessment between the clinical and the commercial process materials. These assessments utilised multiple orthogonal analytical methods capable of supporting a qualitative and quantitative assessment of DP attributes including higher order structure, product-related substances and impurities, general DP attributes, and strengths.

The AZD1222 DP analytical comparability approach is summarised in Table 5. The DP release and characterisation methods selected for the comparability assessment are also indicated.

Table 5 Comparability Assessment of AZD1222 Processes 1, 2, 3 Drug Product

Category	Test	Assessment Criteria and Rationale
General	Appearance	Meet specifications
	pH	
	Osmolality	
	Endotoxin	
	Sterility	
Drug Product attributes	Subvisible particles	Meet compendia limits
	Polysorbate 80 concentration	Consistent with historical range. Observed difference, if any, is not expected to negatively impact product stability
	Extractable volume	Meet specification. Clinical vial configurations and nominal volumes are different by design to meet the respective clinical study needs
Strength	Viral particle concentration by AEX	Report results. Clinical dosing volume is set based on the DP concentration
	Viral genome copy by qPCR	
	Infectivity	
Higher order structure	Viral particle size by NTA	Consistent viral particle size/mass within assay variability
	Viral particle molar mass by FFF-MALS	
Product-related substances or impurities	DNA: Protein by A_{260}/A_{280} ratio	Consistent with historical range
	Viral particles: Infectious particles (P:I)	
	Viral particle aggregates by A_{320}/A_{260}	

AEX = anion exchange chromatography; DP = Drug Product; FFF-MALS = field flow fractionation multi-angle light scattering; NTA = nanoparticle tracking analysis

Source: Table 1, P.2.3.3

4.1 Comparative testing results

Concentration of DP lots by Process 1, Process 2, and Process 3 were determined using different sets of analytical methods (Table 6). Specifically, strengths of Process 1 DP lots were measured using the UV spectroscopic method (A_{260}) for viral particle concentration and the CBF infectivity method for infectious particle concentration. The target clinical dosage of Process 1 (CBF) DP was 5×10^{10} vp per dose based on the viral particle concentration by UV A_{260}.

Concentration of Process 2 DP lots were measured by Advent using their qPCR method for viral genome copy determination and the Advent infectivity method for infectious particles concentration. Lot release of Process 2 DP lots at Advent did not include the determination of viral particle concentration by UV A_{260} and the target clinical dosage of Process 2 (Advent) DP was 5×10^{10} viral genome copies per dose based on the viral genome concentration by Advent qPCR.

Concentration of Process 3 DP lots were measured using the UV spectroscopic method (A_{260}) for viral particle concentration, the Advent qPCR method for viral genome copy, and the Advent infectivity method for infectious particle concentration. The target clinical dosage of Process 3 (Cobra/Symbiosis) DP is $3.5 – 6.5 \times 10^{10}$ viral particles per dose based on the vp/mL concentration determined by UV A_{260}, with a 0.5 mL dosing volume. This dosing range is based on a target 5×10^{10} viral particles per dose and a ± 30% range to take into account process and method variabilities.

For the purpose of the analytical comparability assessment between Process 1, Process 2, and Process 3 DP, the same set of analytical methods were applied as indicated in Table 6, ie, viral particle concentration (vp/mL) by the proposed commercial specification AEX method, viral genome copy (vg/mL) by an improved qPCR method, and infectious particle concentration (ifu/mL) by the proposed commercial specification infectivity method. In the case of K.0007, the dosage evaluated in the comparability assessment was a SD based on Advent qPCR concentrations.

Table 6 Testing Methods of Strengths Related Attributes for AZD1222 Processes 1, 2, 3 DP

Test	Lot Release Testing Method			Comparability Testing Method		
	Process 1	Process 2	Process 3	Process 1	Process 2	Process 3
UV A_{260}	√ (CBF)	--	√ (SGS)	--	--	--
qPCR	--	√ (Advent)	√ (Advent)	√ (Commercial)	√ (Commercial)	√ (Commercial)
Infectivity	√ (CBF)	√ (Advent)	√ (Advent)	√ (Commercial)	√ (Commercial)	√ (Commercial)
AEX	--	--	--	√ (Commercial)	√ (Commercial)	√ (Commercial)

AEX = anion exchange chromatography; CBF = Clinical BioManufacturing Facility; SGS = Contract laboratory
Source: Table 3, P.2.3.3

Differences in strength was further examined for potential impact on clinical dosing by taking into account the clinical dosing volume (for SD) of each DP lot (Table 7). As can be seen in Table 7, the resulting Process 3 DP dosage at 0.5 mL are consistent with the Process 1 and Process 2 DP dosing ranges for all 3 different measures of strengths, viral particle per dose, viral genome copy per dose, and infectious particle per dose. Three Process 3 DP lots have viral particle per dose of 4.0×10^{10} that was slightly outside the Process 1 and Process 2 DP dosing range of $4.6 – 6.0 \times 10^{10}$ vp/dose; and 3 Process 3 DP lots had infectious particle per dose of 4.4×10^{8}, 4.7×10^{8}, and 7.7×10^{8} ifu/mL, that were slightly outside the Process 1 and Process 2 DP dosing range of $4.9 – 7.3 \times 10^{8}$ ifu/mL. These differences were considered to be comparable to or within the variabilities from the analytical methods used in concentration determination and the dosing volumes during clinical administration. The dosing volume for K.0007 in Table 7 was based on the Advent qPCR concentration (ie, SD). The equivalent DP volume per dose for participants who received LD of this lot is 0.13 mL. Therefore, the LD administered would be approximately 45% that of the SD.

Table 7 Clinical Strengths of AZD1222 Drug Product

Process	Lot	Study	Equivalent DP Volume per Dose (mL)	Viral Particle per Dose (vp)	Viral Genome Copy per Dose (vg)	Infectious Particle per Dose (ifu)
Process 1 (CBF)	02P20-01	COV001	0.34	5.1×10^{10}	4.7×10^{10}	7.2×10^{8}
Process 2 (Advent)	K.0007	COV002	0.29	5.6×10^{10}	4.1×10^{10}	5.6×10^{8}
	K.0008	COV002, COV003, COV005	0.24	4.6×10^{10}	3.4×10^{10}	4.9×10^{8}
	K.0009	COV001 COV002, COV003, COV004	0.36	5.7×10^{10}	4.0×10^{10}	7.3×10^{8}
	K.0011	COV004, COV005	0.5	6.0×10^{10}	2.9×10^{10}	5.4×10^{8}
Process 3 (Symbiosis)	20481A	D8110C00001	0.5	5.5×10^{10}	3.3×10^{10}	6.4×10^{8}
	20481B	D8110C00001	0.5	4.0×10^{10}	3.2×10^{10}	4.4×10^{8}
	20482A	D8110C00001	0.5	5.5×10^{10}	3.4×10^{10}	6.3×10^{8}
	20482B	COV001, COV002, COV003, COV004, D8110C00002	0.5	5.5×10^{10}	3.9×10^{10}	4.9×10^{8}
	20482C	COV003, D8110C00001, COV005	0.5	5.0×10^{10}	3.6×10^{10}	6.1×10^{8}
	20492	D8110C00001	0.5	5.5×10^{10}	3.9×10^{10}	7.7×10^{8}
	20495	COV001, COV003, D8110C00001, D8110C00002	0.5	5.5×10^{10}	4.0×10^{10}	5.9×10^{8}
	20497	D8110C00001	0.5	5.5×10^{10}	3.9×10^{10}	5.9×10^{8}
	20503	D8110C00001	0.5	4.0×10^{10}	3.2×10^{10}	4.7×10^{8}
	20506	D8110C00001, COV002, COV004	0.5	4.0×10^{10}	3.3×10^{10}	5.0×10^{8}

CBF = Clinical BioManufacturing Facility; DP = Drug Product; vg = viral genome; ifu = infectious unit; vp = viral particle
Source: Table 4, P.2.3.3

Comparative physicochemical characteristics of the Process 1 (CBF), Process 2 (Advent S.R.L, Advent), and Process 3 (Cobra/Symbiosis Pharmaceutical Services, Symbiosis) DP lots are shown in Table 8.

Table 8 Comparison of AZD1222 Processes 1, 2, 3 Drug Product Lot test results (Physicochemical properties)

Process	Lot	Testing Results							
		Appearance [a]	**pH**	**Osmolality (mOsmol/kg)**	**Endotoxin (EU/mL)**	**Sterility**	**Subvisible Particles (particles/container)**	**PS-80 Concentration % (w/v)**	**Extractable Volume [d]**
Process 1 (CBF)	02P20-01	Slightly opaque, essentially particle free	6.59	425.3	< 1.00	Pass	NT	0.11	NT
	02P20-02	Slightly opaque, essentially particle free	6.55	427	< 1.00	Pass	NT	NT	NT
Process 2 (Advent)	K.0007	Clear solution essentially free from visible particles	6.6	418	< 1.00	Absence of growth	NT	0.21	1.08 mL
	K.0008	Clear solution essentially free from visible particles	6.5	416	< 0.500	Absence of growth	NT	0.21	1.08 mL
	K.0009	Clear solution essentially free from visible particles	6.5	418	< 0.500	Absence of growth	≥ 2 µm: 194 ≥ 5 µm: 26 ≥ 10 µm: 3 ≥ 25 µm: 0	0.18	1.08 mL
	K.0011	Clear solution essentially free from visible particles	6.5	405	< 0.0500	Absence of growth	NT	0.10	1.12 mL

Table 8 Comparison of AZD1222 Processes 1, 2, 3 Drug Product Lot test results (Physicochemical properties)

Process	Lot	Testing Results								
		Appearance [a]	pH	Osmolality (mOsmol/kg)	Endotoxin (EU/mL)	Sterility	Subvisible Particles (particles/container)		PS-80 Concentration % (w/v)	Extractable Volume [d]
Process 3 (Cobra/Symbiosis)	20481A	Meets specifications	6.6	420	< 10	No growth	≥ 2 µm	2614	0.12 [b]	Meets specification
							≥ 5 µm	401		
							≥ 10 µm	52		
							≥ 25 µm	1		
	20481B	Meets specifications	6.6	419	< 0.05	No growth	≥ 2 µm	1178	0.12 [b]	Meets specification
							≥ 5 µm	284		
							≥ 10 µm	46		
							≥ 25 µm	3		
	20482A	Meets specifications	6.6	420	< 0.5	No growth	≥ 2 µm	1967	0.12 [b]	Meets specification
							≥ 5 µm	322		
							≥ 10 µm	50		
							≥ 25 µm	0		
	20482B	Meets specifications	6.6	419	0.57	No growth	≥ 2 µm	1050	0.12 [b]	Meets specification
							≥ 5 µm	215		
							≥ 10 µm	20		
							≥ 25 µm	0		
	20482C	Meets specifications	6.6	419	< 0.5	No growth	≥ 2 µm	2067	0.12 [b]	Meets specification
							≥ 5 µm	345		
							≥ 10 µm	45		
							≥ 25 µm	1		

Table 8 Comparison of AZD1222 Processes 1, 2, 3 Drug Product Lot test results (Physicochemical properties)

Process	Lot	Testing Results								
		Appearance [a]	pH	Osmolality (mOsmol/kg)	Endotoxin (EU/mL)	Sterility	Subvisible Particles (particles/container)		PS-80 Concentration % (w/v)	Extractable Volume [d]
Process 3 (Symbiosis)	20492	Meets specifications	6.6	414	< 0.05	No growth	≥ 2 µm	1429	0.12 [c]	Meets specification
							≥ 5 µm	274		
							≥ 10 µm	50		
							≥ 25 µm	0		
	20495	Meets specifications	6.7	416	< 0.5	No growth	≥ 2 µm	1216	0.12 [c]	Meets specification
							≥ 5 µm	202		
							≥ 10 µm	33		
							≥ 25 µm	1		
	20497	Meets specifications	6.6	419	< 0.5	No growth	≥ 2 µm	2197	0.12 [c]	Meets specification
							≥ 5 µm	438		
							≥ 10 µm	80		
							≥ 25 µm	1		
	20503	Meets specifications	6.6	419	< 0.5	No growth	≥ 2 µm	2094	0.12 [c]	Meets specification
							≥ 5 µm	500		
							≥ 10 µm	148		
							≥ 25 µm	0		
	20506	Meets specifications	6.6	419	0.5	No growth	≥ 2 µm	2409	0.12 [c]	Meets specification
							≥ 5 µm	551		
							≥ 10 µm	185		
							≥ 25 µm	3		

CBF = Clinical BioManufacturing Facility; NT = not tested; PS-80 = polysorbate 80

[a] Meets Specifications (Appearance) = Clear to slightly opaque solution, practically free from visible particles

[b] Polysorbate 80 (% w/v) determined on source Drug Substance lot AS/00001/07/A. DP was produced by filling the source DS without dilution.

[c] Polysorbate 80 (% w/v) determined on source Drug Substance lot AS/00001/07/C. DP was produced by filling the source DS without dilution.

[d] Meets Specifications (Extractable Volume) = Not less than labelled volume

Source: Table 2, P.2.3.3

Table 9 Comparison of AZD1222 Processes 1,2,3 Drug Product lot test results (Table 8 continued)

Lot	Testing Results							
	Viral Particle Concentration by AEX (vp/mL)	**Viral Genome Copy by qPCR (vg/mL)**	**Infectious Particle Concentration by Infectivity (ifu/mL)**	**Viral Particle Size by NTA (nm)**	**Viral Particle Molar Mass by FFF-MALS (MDa)**	**DNA: Protein by A_{260}/A_{280} ratio**	**Viral Particle: Infectious Particle Ratio (vp/ifu)**	**Viral Particle Aggregates by A_{320}/A_{260}**
02P20-01	1.5×10^{11}	1.37×10^{11}	21.29×10^{8}	90	102	1.3	70	0.22
K.0007	1.9×10^{11}	1.38×10^{11}	18.88×10^{8}	89	128	1.3	101	0.16
K.0008	1.9×10^{11}	1.42×10^{11}	20.44×10^{8}	91	124	1.3	93	0.16
K.0009	1.6×10^{11}	1.12×10^{11}	20.56×10^{8}	90	105	1.3	78	0.15
K.0011	1.2×10^{11}	5.70×10^{10}	10.86×10^{8}	89	103	1.3	110	0.20
20481A	1.1×10^{11}	6.60×10^{10}	12.81×10^{8}	90	96.4	1.3	86	0.20
20481B	0.8×10^{11}	6.33×10^{10}	8.7×10^{8}	92	110.6	1.3	92	0.22
20482A	1.1×10^{11}	6.70×10^{10}	12.69×10^{8}	91	110	1.3	87	0.20
20482B	1.1×10^{11}	7.78×10^{10}	9.7×10^{8}	89	102	1.3	113	0.21
20482C	1.0×10^{11}	7.27×10^{10}	12.2×10^{8}	88	118	1.3	82	0.22
20492	1.1×10^{11}	7.78×10^{10}	15.4×10^{8}	88	121	1.3	71	0.23
20495	1.1×10^{11}	8.05×10^{10}	11.8×10^{8}	89	125	1.3	93	0.22
20497	1.1×10^{11}	7.83×10^{10}	11.8×10^{8}	89	129	1.3	93	0.23
20503	0.8×10^{11}	6.40×10^{10}	9.3×10^{8}	91	119	1.3	86	0.25
20506	0.8×10^{11}	6.67×10^{10}	9.9×10^{8}	92	111	1.3	81	0.26

AEX = anion exchange chromatography; ifu = infectious units; FFF-MALS = field flow fractionation multi-angle light scattering; NT = not tested; NTA = nanoparticle tracking analysis; vg = viral genome copy; vp = viral particle

Source: Table 2, P.2.3.3

All results meet the comparability assessment criteria provided in Table 5. Differences in strength related attributes (ie, viral particle concentration, viral genome concentration, and infectious particle concentration) were observed. The clinical dosage by taking into account the corresponding dosing volume (for SD) of each DP lot, however, are comparable. In conclusion, results from these comparative testing demonstrate the analytical comparability between AZD1222 Process 1, Process 2, and Process 3 DP.

5 CONCLUSION

Comparative analyses revealed that there were no meaningful differences between the SD delivered using the Advent material when the volume was adjusted and the Cobra/Symbiosis as measured by viral particles, infectious particles per dose, and the Viral particles: Infectious particles (P:I) ratio. These comprehensive comparative analyses across manufacturing processes led to the identification of an unexpected interference of an excipient with the spectrometry assay resulting in dose miscalculation in Group 4 participants in the COV002. The Process 2 DP (Advent lot #s K.0007, K.0008, and K.0009) used in the COV002 study had almost twice the concentration of Polysorbate 80 % (w/v) (Table 8). During the conduct of the study, the testing method applied by CBF to determine concentration did not account for the effect of the higher concentration of PS80 in the DP. 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 ~ half (45%) the intended dose for administered to 1716 of participants in Group 4 of COV002 study.

Similarly, discrepancy between results obtained for the concentration of DP for Advent lot K.0011 by 3 PCR technologies (1 by Advent and 2 by AZ) resulted in the administration of lower doses in few participants in the COV005 study. Subsequent to this identification dose volume was adjusted to provide a SD of 5 x 10^{10} vp. A suite of assays have now been developed for 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 x 10^{10} vp.

6 REFERENCES

Voysey 2020

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Justification for Missing Studies	
Drug Substance	AZD1222
Date	19 December 2020

Justification for Missing Studies

AZD1222 – Prevention of COVID-19

1 JUSTIFICATION FOR CLINICAL STUDIES NOT INCLUDED IN THE MARKETING AUTHORISATION APPLICATION

The COVID-19 AstraZeneca Vaccine (hereafter referred to as AZD1222) is indicated for active immunisation of individuals ≥18 years for the prevention of COVID-19. There is a justification for some clinical studies that were not required to be conducted and, therefore, some of the CTD Module 5 sections are not populated in this application.

Table 1 provides a listing of sections in Module 5 of this CTD that do not contain studies which otherwise might be relevant to an application. These listings are accompanied by the applicant's justification for each section within the module that does not include a CSR.

Table 1 Listing of sections in Module 5 of the CTD that do not contain reports

Section	Section title	Justification
5.3.1.1	Bioavailability study reports	AZD1222 is administered as an intramuscular injection of 5×10^{1}□ virus particles. Bioavailability studies would thus be irrelevant and are not required.
5.3.1.2	Comparative bioavailability and bioequivalence study reports and information	AZD1222 is administered as an intramuscular injection. The clinical biopharmaceutics program for the vaccine, therefore, did not assess absolute bioavailability, nor was there an assessment of the effect of food on bioavailability.
5.3.1.3	*In vitro, in vivo* correlation study reports	AZD1222 is administered as an intramuscular injection. Therefore, *in vitro* and *in vivo* correlation studies were not required.
5.3.2	Reports of studies pertinent to pharmacokinetics using human biomaterials	Because AZD1222 is a chimpanzee adenovirus viral vector vaccine, no *in vitro* permeability, *in vitro* metabolism, or *in vitro* metabolic drug-drug interaction studies using human biomaterials were performed for this program.
5.3.3.1	Healthy subject PK and initial tolerability study reports	Pharmacokinetic assessments are not applicable; data regarding AZD1222 safety, tolerability and immunogenicity are presented elsewhere in this submission.
5.3.3.2	Patient PK and initial tolerability study reports	Pharmacokinetic assessments are not applicable; data regarding AZD1222 safety, tolerability and immunogenicity are presented elsewhere in this submission.
5.3.3.3	Intrinsic factor PK study reports	Pharmacokinetic assessments are not applicable; demographic characteristics of the study population and analyses by population subgroups and the role of other potential covariates are presented elsewhere in this submission.
5.3.3.4	Extrinsic factor PK study reports	Pharmacokinetic assessments are not applicable; demographic characteristics of the study population and analyses by population subgroups and the role of other potential covariates are presented elsewhere in this submission.
5.3.4.1	Healthy subject PD and PK/PD study reports	Pharmacokinetic assessments are not applicable; data regarding AZD1222 immunogenicity, the study population and the role of potential covariates are presented elsewhere in this submission.
5.3.4.2	Patient PK and PK/PD study reports	Pharmacokinetic assessments are not applicable; data regarding AZD1222 immunogenicity, the study population and the role of potential covariates are presented elsewhere in this submission.

Table 1 Listing of sections in Module 5 of the CTD that do not contain reports

Section	Section title	Justification
5.3.5.1	Study reports of controlled clinical studies pertinent to the claimed indication	Individual studies have not reached analyses-defined timepoints for reporting other than for the pooled analysis. Clinical study protocols and their respective statistical analysis plans are provided for reference in this section.
5.3.5.2	Study reports of uncontrolled clinical studies	No study has reached analyses-defined timepoint for reporting, and no separate clinical study reports were, therefore, prepared for inclusion in this section.
5.3.5.4	Other study reports	No clinical study reports for the ongoing trials are included in this application; therefore, this section is not applicable.
5.3.6	Reports of postmarketing experience	AZD1222 has not been marketed in any country; therefore, no post-marketing reports are available.
5.3.7	Case report forms and individual patient listings	Case report forms and individual patient listings will be available upon request.

CSR=clinical study report; CTD=Common Technical Document; PD=pharmacodynamic; PK=pharmacokinetic.