2.5 Clinical Overview

Drug Substance AZD1222

Date 25 February 2021

2.5 Clinical Overview

AZD1222 Marketing Authorisation Application

Primary Analysis (Data Cut-off 07 December 2020)

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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).
CSP	Clinical study protocol
DCO	Data cut-off
DP	Drug Product
EDTA	edetate disodium
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
GMFR	geometric mean fold rise
GMR	geometric means response
GMT	geometric mean titre
HAdV-4	Human adenovirus 4
HIV	human immunodeficiency virus
ICH	international council for harmonisation

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

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

CONVENTIONS

Cross-referencing to other documents

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

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

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

Data cut-off dates

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

EXECUTIVE SUMMARY

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

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

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

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

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

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

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

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Pharmacological Class

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

1.2 Indication and Dosing

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

1.3 Scientific Background and Unmet Medical Need

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

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

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

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

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

1.3.1 Rationale for the Development of AZD1222

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

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

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

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

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

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

Non-clinical data

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

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

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

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

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

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

1.4 Clinical Development Programme

1.4.1 Programme Overview

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

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

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

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

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

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

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

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

Table 2 Additional Studies in the Clinical Programme[a]

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

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

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

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

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

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

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

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

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

1.5 Compliance with Regulatory Guidance and Good Clinical Practice

1.5.1 Consultations with Regulatory Authorities Relevant to this Application

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

Table 3 Summary of consultations with regulatory authorities

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

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

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

1.5.2 Compliance with Good Clinical Practice

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

2 OVERVIEW OF BIOPHARMACEUTICS

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

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

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

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

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

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

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

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

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

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

Table 4 Drug Product Development Summary

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

Table 4 Drug Product Development Summary

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

PS-80 = polysorbate 80; vp = viral particles

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

3 OVERVIEW OF CLINICAL PHARMACOLOGY

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

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

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

3.1 Chimpanzee Adenoviral Vectors

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

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

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

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

3.1.1 Anti-vector Immunity

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

3.2 Mechanism of Action

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

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

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

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

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

3.3 Dose and Regimen Selection

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

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

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

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

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

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

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

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

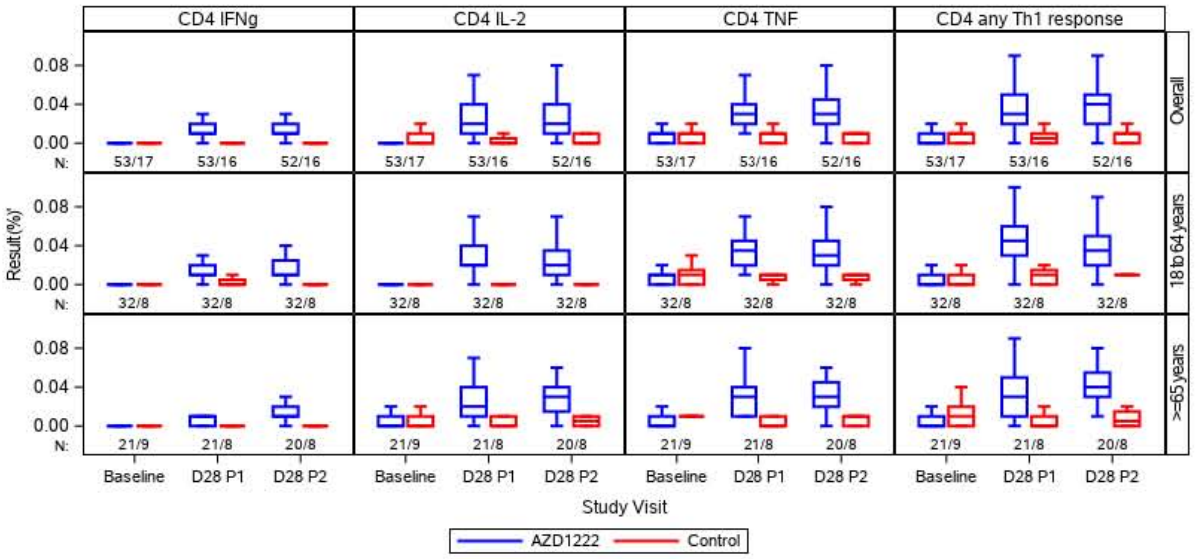
3.4 Cell-mediated Immunity

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

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

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

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



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

4 OVERVIEW OF EFFICACY

4.1 Introduction

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

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

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

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

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

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

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

Table 5 Case Definitions for Evaluation of Efficacy

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

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

4.1.1 Statistical Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.2 Efficacy Results

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

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

4.2.1 Participant Population Studied

4.2.1.1 Participant Disposition

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

Table 6 Disposition of Participants in Pooled Analysis Sets

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

Table 6 Disposition of Participants in Pooled Analysis Sets

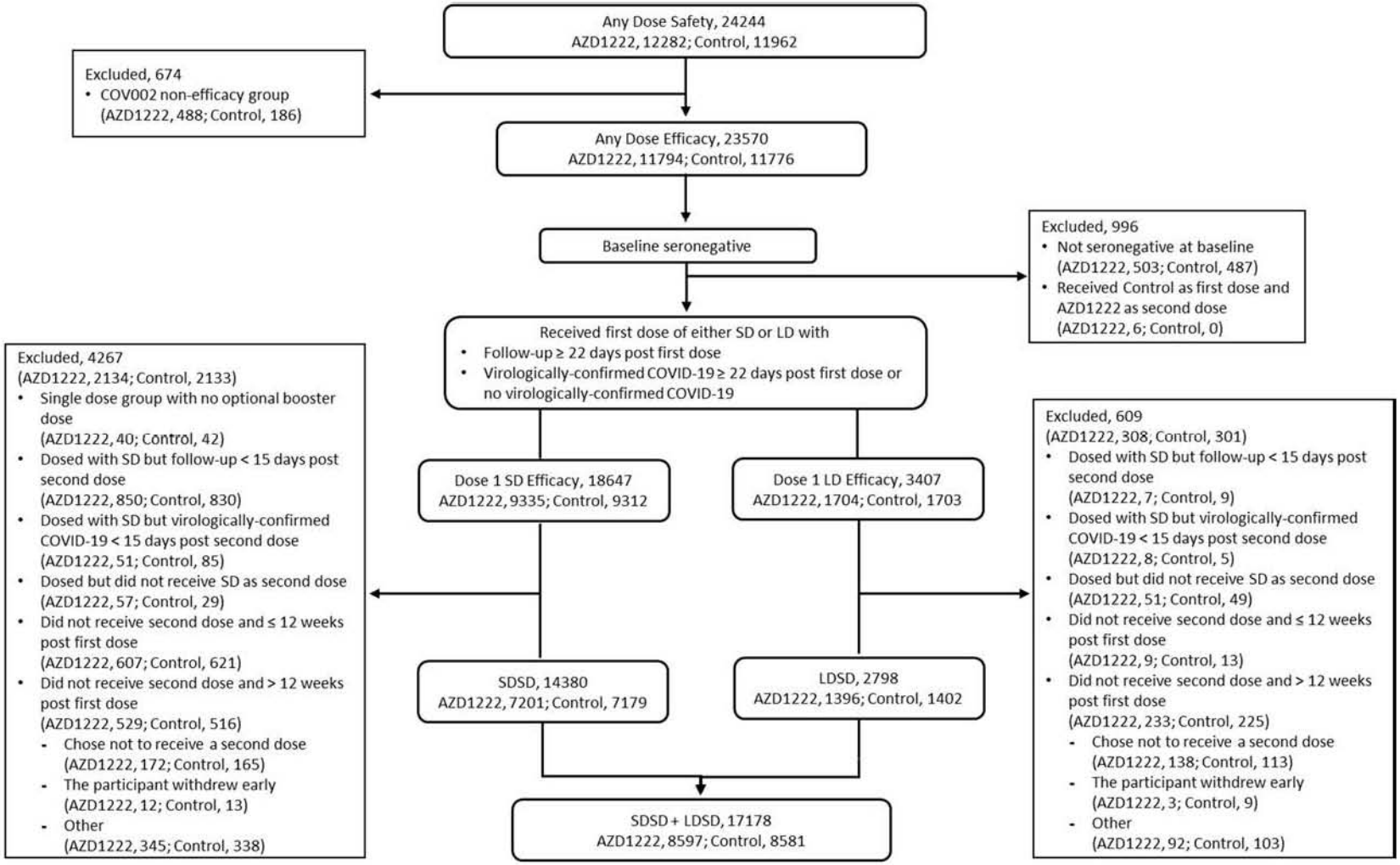
Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	Control	Total
Dose1 LD Seronegative for Efficacy	As treatment received	Seronegative	LDSD LD single dose LDLD	From 22 days post Dose 1	1604 (13.9)	1703 (14.2)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

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

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

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

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



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

Source: Main Safety Tables 1.1.1.1 and 1.1.2.1.

4.2.1.2 Exposure to AZD1222

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

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

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

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

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

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

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

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

4.2.1.3 Demographics and Baseline Characteristics

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

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

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

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

4.2.2 Efficacy Against COVID-19

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

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

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

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

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

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

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

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

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

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

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

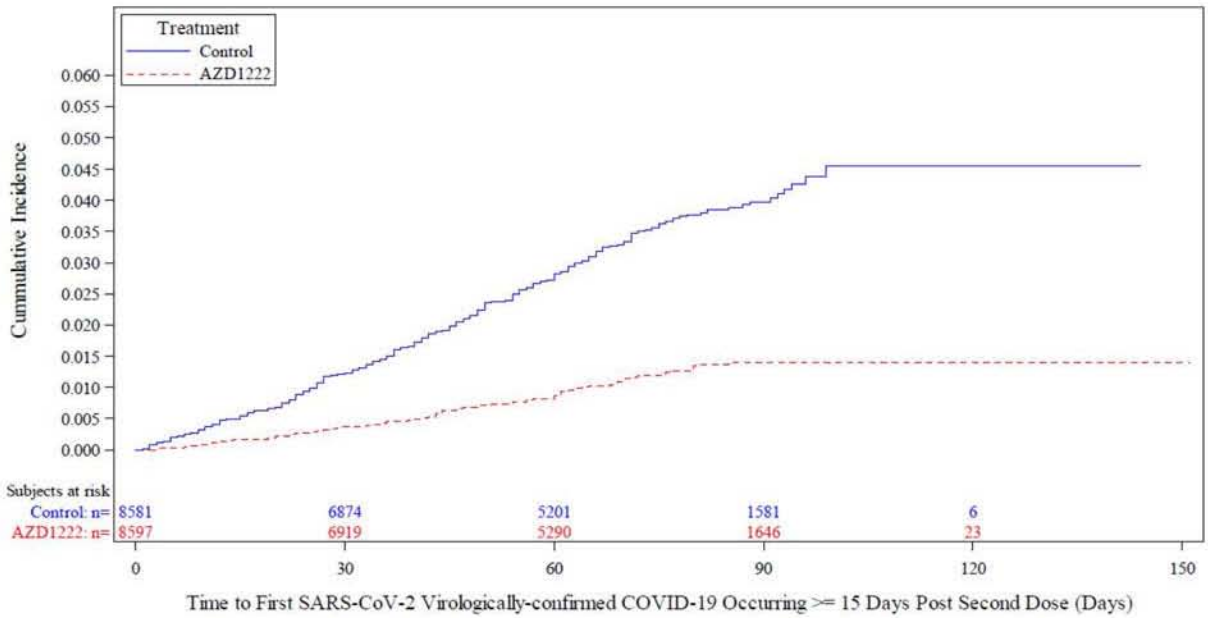
VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from stratified Poisson regression with Exact Conditional Method. The 95% (or 97.5% one-sided) CI for the VE is obtained by taking 1 minus the 95% (or 97.5%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

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

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

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

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

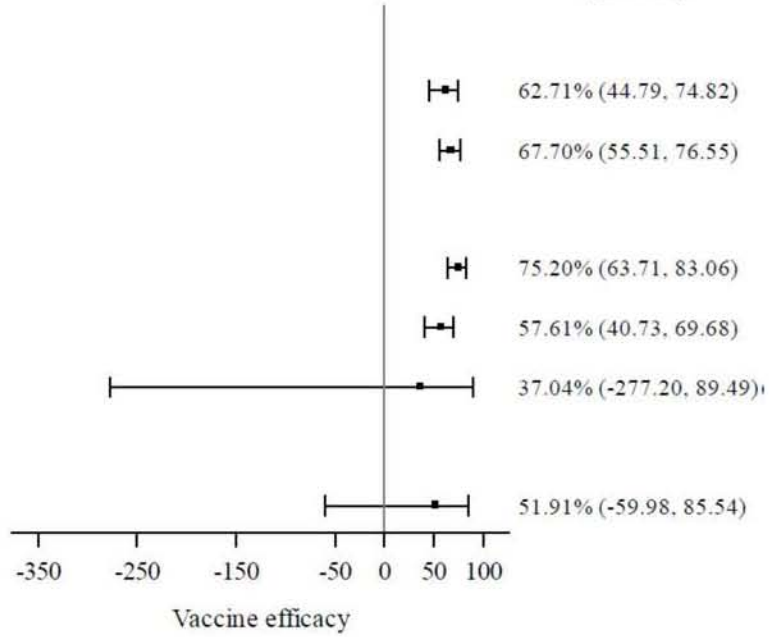


The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring ≥ 15 days post second dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of second dose of study intervention + 15) +1. For censored participants, the censoring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

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

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

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



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

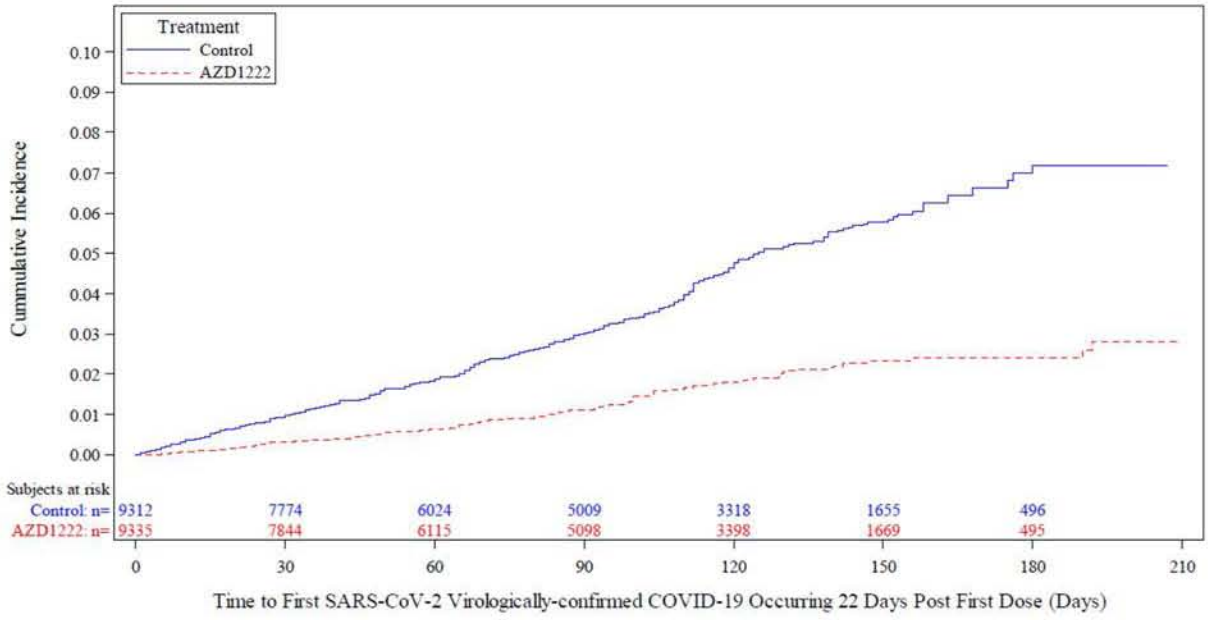
4.2.2.2 Efficacy Against COVID-19 Following First Dose

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

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

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

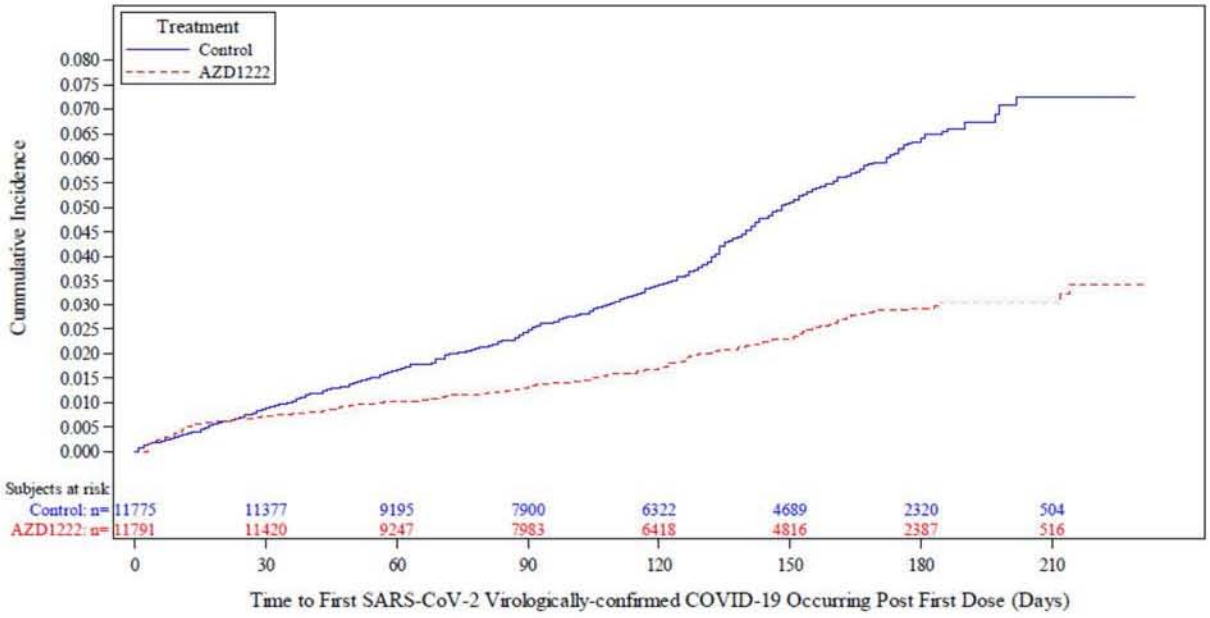
Figure 5 Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed COVID -19 Occurring 22 Days Post First Dose of Study Intervention (Dose 1 SD Seronegative for Efficacy Analysis Set)



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

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

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



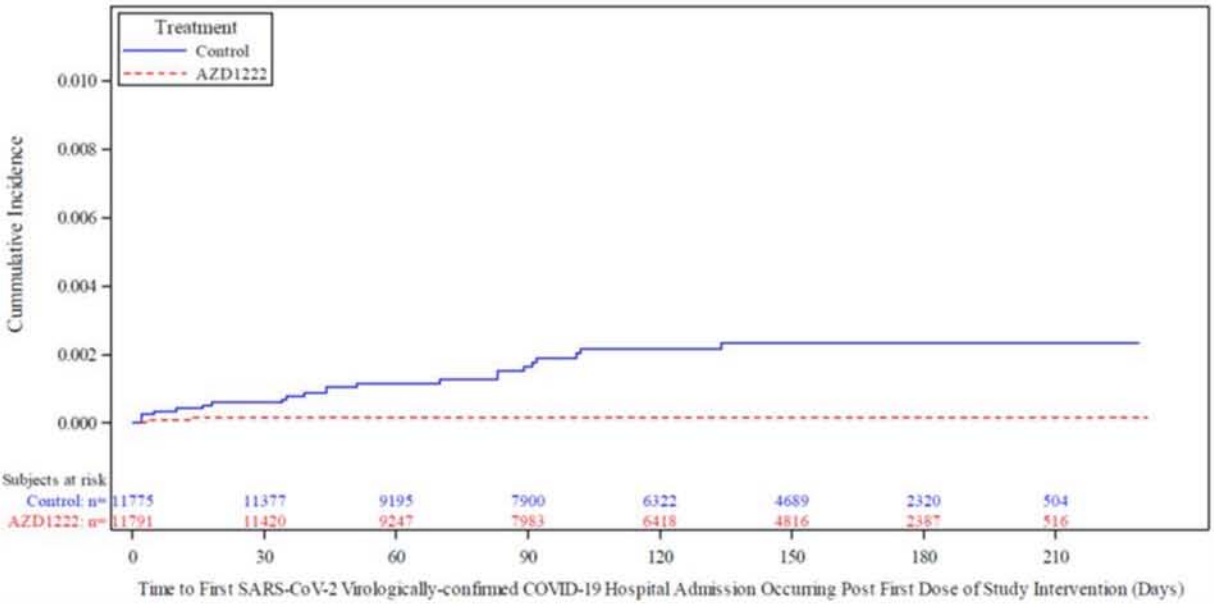
The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of first dose of study intervention +1. For censored participants, the censoring time is from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

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

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

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

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



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

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

Table 9 Vaccine Efficacy Against COVID-19 Hospital Admissions

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

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

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

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

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

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

Table 10 Vaccine Efficacy Against COVID-19 Severe Disease

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

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

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

COVID-19 endpoints were based on adjudicated events.

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

4.2.4 Efficacy Against SARS-CoV-2 Infection

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

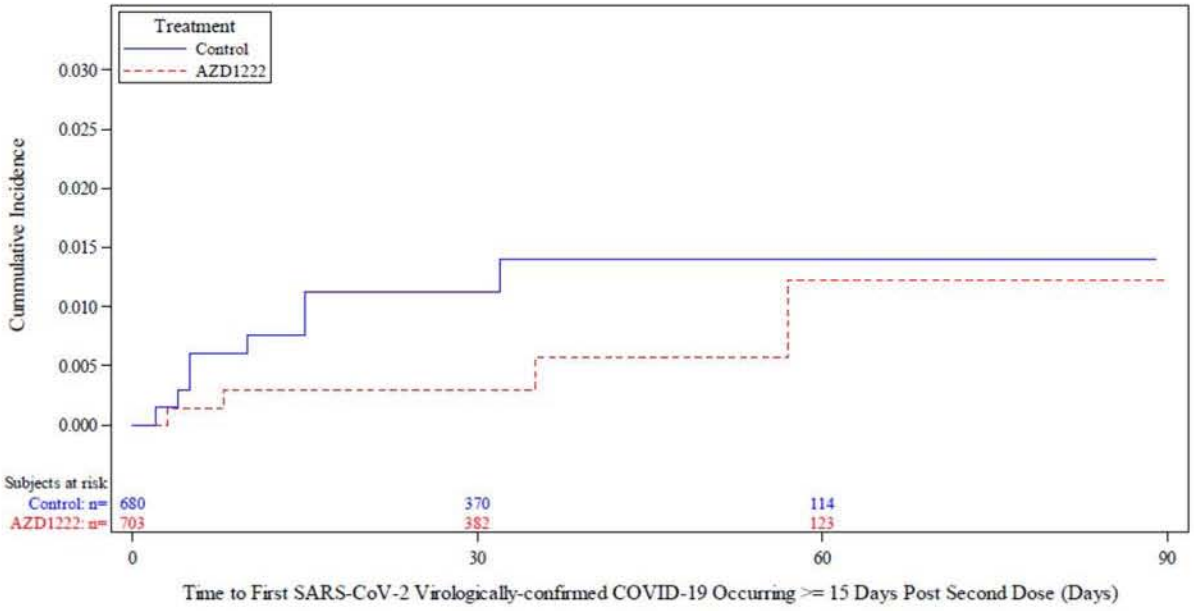
Table 13 Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose in the Age Subgroup ≥ 65 Years (SDSD Seronegative for Efficacy Analysis Set, SDSD Seronegative for Efficacy Analysis Set, Dose Interval 4-12 Weeks)

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

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

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

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



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

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

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

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

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

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

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

COVID-19 endpoints were based on adjudicated events.

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

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

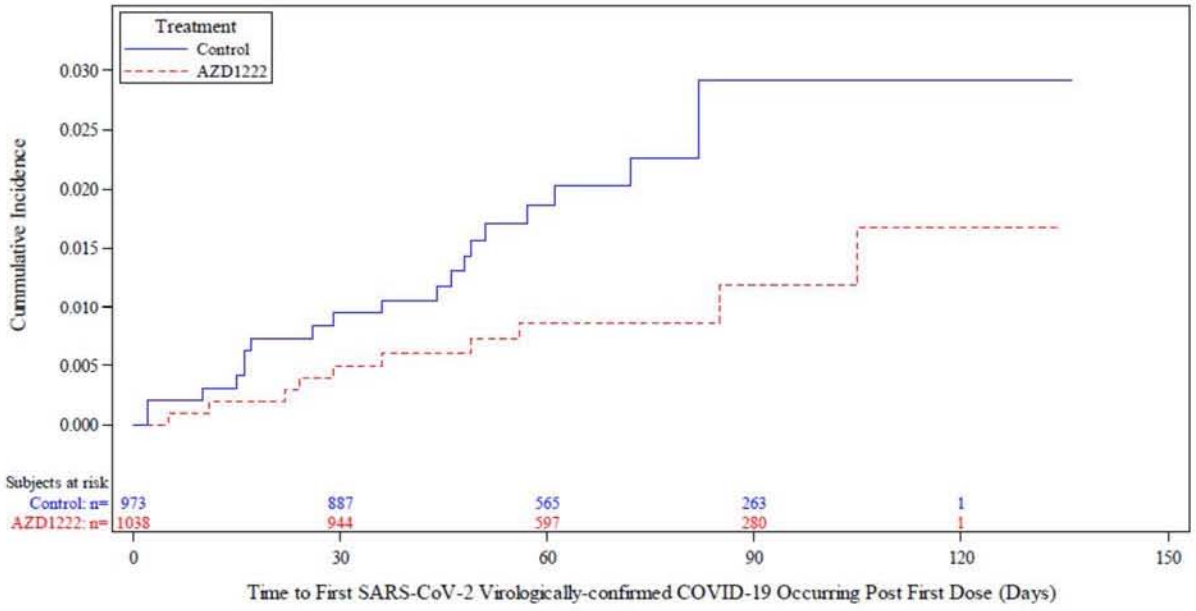
COVID-19 case definition	Participants with events, n (%)		VE (%)	95% [a] or 97.5% [b] CI	Nominal p-value
	AZD1222 (N = 1038)	Control (N= 973)			
COVID-19 (primary case definition)	10 (0.96)	20 (2.06)	52.99 [a]	(-0.46, 78.00) [a]	0.051 [a]
COVID-19 hospitalisation	0	4 (0.41)	100 [b]	(-42.00, NE) [b]	0.110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

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

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

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

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



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

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

4.2.7 Efficacy by Country

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

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

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

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

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

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

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

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

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

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

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

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

COVID-19 endpoints were based on adjudicated events.

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

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

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

4.2.8 Humoral Immunogenicity

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

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

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

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

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

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

4.2.8.1 Rate of Seroconversion

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

4.2.8.2 Quantification of Anti-S and nAb Titres

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

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

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

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

4.2.8.3 Humoral Immune Response by Subcategories

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

Adults with Comorbid Conditions at Baseline

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

Country

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

Older Adults (≥ 65 years of age)

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

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

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

4.2.9 Exploratory Analyses of Dose and Regimen

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

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

4.2.9.1 Effect of Dose Interval on Efficacy

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

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

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

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

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

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

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

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

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

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

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

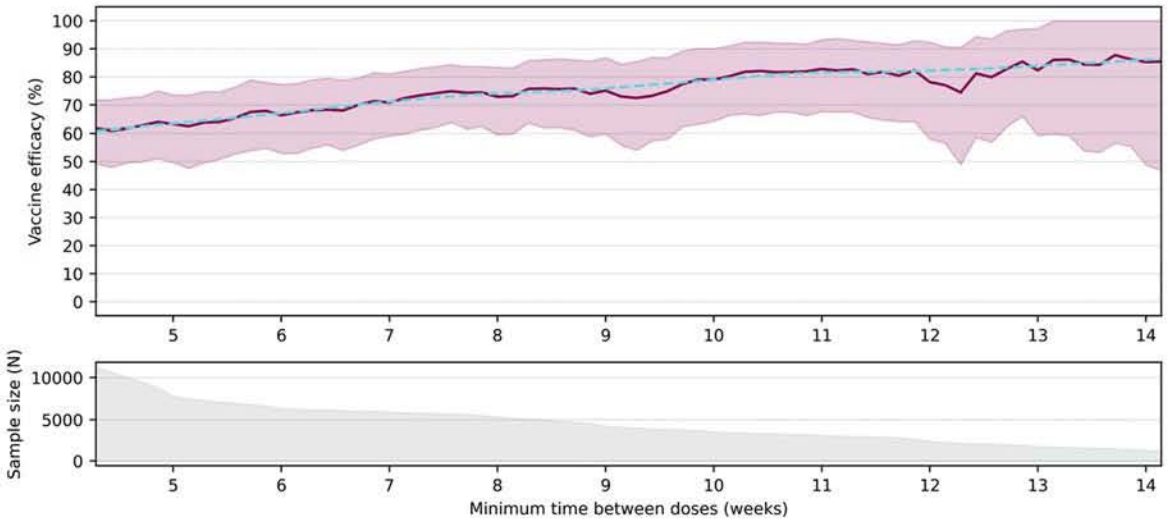
Analysis set Time interval between Dose 1 and Dose 2	Participants with events AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD + LDSD Seronegative for Efficacy Analysis Set					
< 4 weeks	1 / 206 (0.49)	3 / 203 (1.48)	66.56	(-221.83, 96.53)	0.343
≥ 4 to < 8 weeks	47 / 4312 (1.09)	90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

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

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

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

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



Source: data on file.