29 January 2021
EMA/94907/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COVID-19 Vaccine AstraZeneca

Common name: COVID-19 Vaccine (ChAdOx1-S [recombinant])

Procedure No. EMEA/H/C/005675/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE-2	Angiotensin-Converting Enzyme 2
ADE	Antibody-Dependent Enhancement
AdHu	Human Adenovirus
ADME	Absorption, distribution, metabolism, excretion
AEX	Anion exchange chromatography
ARDS	Acute respiratory distress syndrome
AS	Active substance
AUC	Analytical ultracentrifugation -
AZD1222	COVID-19 Vaccine AstraZeneca
BAL	Bronchoalveolar Lavage
BMI	Body mass index
BVH	Bulk viral harvest
BWP	Biological Working Party
ChAd63	Chimpanzee Adenovirus 63
ChAdOx1	Chimpanzee Adenovirus Ox1
ChAdOx1 MERS	Chimpanzee Adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	Name of AZD1222 when initially developed by the University of Oxford
ChAdOx2	Chimpanzee Adenovirus Ox2
CHMP	Committee for Medicinal Products for Human Use
CMV	Cytomegalovirus
CNS	Central Nervous System
COVID-19	Coronavirus disease-2019
CPP	Critical process parameter
CQAs	Critical quality attributes
CT	Computerised Tomography
DART	Developmental and Reproductive Toxicology
DPP4	Dipeptidyl Peptidase 4
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EDTA	Edetate disodium
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immunospot
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERD	enhanced respiratory disease
EU	European Union
FFF	Field flow fractionation
FIH	First in Human
FP	Finished product
g	Guide
GalK	Galactokinase
GFP	Green Fluorescent Protein
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM	Geometric Mean
GMP	Good Manufacturing Practice
HAdV	Human Adenovirus
HAdV5	Human adenovirus serotype 5
HBV	Hepatitis B virus
HCP	Host cell protein
HEK	Human Embryonic Kidney Cells
HIV	Human Immunodeficiency Virus
HRP	Horseradish peroxidase
ICH	International Council for Harmonisation
ICU	Intensive care Unit
IFN γ	Interferon gamma
IgG	Immunoglobulin G

IL	Interleukin
IM	Intramuscular
IN	Intranasal
Inf.U	Infectious units
IPC	In-process controls
LTCF	Long-term care facilities
MAA	Marketing Authorisation Application
MALS	Multi-angle light scattering
MC	Microbial control
MC	Microbial Control
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
ME-TRAP	Multiple epitopes and thrombospondin related adhesion protein
MHCB	Master Host Cell Bank
MHRA	Medicines and Health products Regulatory Agency
MVA	Modified vaccinia virus Ankara
MVM	Minute virus of mice
MVS	Master virus seed
NAb	Neutralising antibody
NAT	Nucleic acid test
NCPP	Non-critical process parameter
NHP	Non-Human Primate
NOAEL	No-observed-adverse-effect level
NP	Influenza A nucleoprotein
NTA	Nanoparticle tracking analysis
OC	Other concern
PA	Performance attribute
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDCO	Paediatric Committee
PFU	Plaque-forming units
Ph. Eur.	European Pharmacopeia
PIP	Paediatric Investigation Plan
PPQ	Process performance qualification
PRAC	Pharmacovigilance Risk Assessment Committee
QC	Quality control
qPCR	Quantitative polymerase chain reaction
RBD	Receptor-binding domain
RCA	Replication competent adenoviruses
RMP	Risk Management Plan
RNA	Ribonucleic acid
RR	Rolling review
RT-PCR	Reverse transcription polymerase chain reaction
S	surface Spike glycoprotein
SAdV	Simian Adenoviruses
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SFC	Spot Forming Cells
sg	single guide
SmPC	Summary of the Products Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCID	Tissue culture infective dose
TCID50	Median Tissue Culture Infectious Dose
TEM	Transmission electron microscopy
Tet	Tetracycline

TFF	Tangential flow filtration
Th	T-Helper Cell
TNFα	Tumour Necrosis Factor alpha
tPA	Tissue plasminogen activator
TSE	Transmissible spongiform encephalopathy
UK	United Kingdom
US	United States
v/v	volume per volume
VED	Vaccine Enhanced Disease
vp	Viral particles
w/v	weight per volume
WHCB	Working host cell bank
WHO	World Health Organisation
WVS	Working virus seeds

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 11 January 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for COVID-19 Vaccine AstraZeneca, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 9 June 2020.

The applicant applied for the following indication:

"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 use of this vaccine should be in accordance with official recommendations".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0003/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in

accordance with Article 14-a of the Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance Chimpanzee adenovirus vector encoding the SARS-CoV-2 spike glycoprotein (ChAdOx1-S) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advices on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
11 September 2020	EMEA/H/SA/4655/1/2020/II	*Ms Rosalia Ruano Camps and Prof Brigitte Schwarzer-Daum*
16 September 2020	EMEA/H/SA/4655/3/2020/I	*Ms Rosalia Ruano Camps and Dr Karin Janssen van Door*
18 September 2020	EMEA/H/SA/4655/2/2020/I	*Ms Rosalia Ruano Camps and Prof Brigitte Schwarzer-Daum*
27 October 2020	EMEA/H/SA/4690/1/2020/II	*Dr Jens Reinhardt and Dr Ingrid Schellens*
28 October 2020	EMEA/H/SA/4655/1/FU/1/2020/II	*Dr Ferran Torres and Dr Ingrid Schellens*

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- *Concurrent and prospective process validation approach*
- *Proposal, after MAA, to release batches for distribution made prior to the initiation of validation, provided that pre-PV lots will demonstrate alignment with the commercial process and meet the approved commercial specifications*
- *Proposed use of a rapid method for sterility testing as an alternative to Ph. Eur. 2.6.1*
- *Preclinical vector biodistribution studies*
- *DART studies*
- *Concurrence that juvenile animal studies are not needed*
- *Provision of published data instead of preclinical studies reports to support regulatory submission*
- *Concurrence that supportive platform information gathered from previous early-phase clinical studies of the vaccine vector in support of the registration of AZD1222 will be submitted in the format of scientific journals*
- *The proposed immunogenicity objectives and the assay methodologies, and validation status*
- *Proposed strategy using pooled efficacy, immunogenicity, and safety data from across the UK Phase I/II Study COV001, UK Phase II/III Study COV002, Brazil Phase III Study COV003, and South Africa*

Phase I/II Study COV005 to support regulatory submission

- *Sufficiency of data from interim analyses for regulatory decision*
- *Statistical analysis plan*
- *Acceptability of pooled datasets from HD/HD and from LD/HD under the condition that immunogenicity is similar across various subsets*
- *Risk management plan*
- *Signal detection strategy*

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sol Ruiz Co-Rapporteur: Johann Lodewijk Hillege

The CHMP confirmed eligibility to the centralised procedure on	09 June 2020
The ETF recommended to start the rolling review procedure on	22 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	30 September 2020
The procedure (Rolling Review 1) started on	01 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	15 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	27 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion (Rolling Review 1) via 24 hour written procedure on	06 November 2020

The applicant submitted documentation as part of a rolling review 2 on non-clinical and quality data to support the marketing authorisation application	11 December 2020
The procedure (Rolling Review 2) started on	12 December 2020
The applicant submitted documentation as part of a rolling review (Rolling Review 3) on clinical data (clinical and RMP) to support the marketing authorisation application	24 December 2020
The procedure (Rolling Review 3) started on	24 December 2020
The Rapporteurs circulated ERA Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 December 2020
ETF discussions took place on	07 January 2021
Adoption of second Interim Opinion (Rolling Reviews 2 and 3) via 24 hour written procedure on	09 January 2021
The application for the conditional marketing authorisation was formally received by the EMA on	11 January 2021
The procedure started on	12 January 2021
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: 1. 'Catalent Maryland Harmans (BWI),7555, Harmans Road, Harmans, Maryland 21077, USA' proposed as drug substance manufacture and 2. 'Catalent Località Fontana del Ceraso, S.P. Casilina 12 n. 41, 03012 Anagni FR, Italy' proposed as drug product manufacture and QC testing site.	1. 14-17 December 2020 2. 30 November - 03 December 2020
BWP extraordinary adobe meeting was held on	13 January 2021
The CHMP rapporteur's and co-rapporteurs Assessment Reports were circulated to all CHMP, PRAC, BWP, peer reviewer and ETF on	18 January 2021
The PRAC rapporteur's Assessment Report was circulated to all CHMP, PRAC and ETF on	18 January 2021
BWP meeting was held on	19 January 2021
ETF discussions took place on	21 January 2021
BWP extraordinary meeting was held on	22 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary PRAC meeting on	22 January 2021
ETF discussions took place on	22 January 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 January 2021

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to COVID-19 Vaccine AstraZeneca during the CHMP meeting on	29 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

End of December 2019, World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020 the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally and on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to ECDC, histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 29 January 2021, there have been over 101 million confirmed cases of SARS-CoV-2 infection globally with approximately 2.1 million deaths resulting from infection and subsequent coronavirus disease (COVID-19). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities.

Increasing age is another risk factor for severe disease and death due to COVID-19. European countries that have established surveillance systems in long-term care facilities (LTCF) have reported that 5-6% of all current LTCF residents died of COVID-19, and that LTCF residents accounted for up to 72% of all COVID-19 related deaths.

Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell

membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for vaccines able to prevent or mitigate COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a

population level are desired. Although two vaccines for prevention of COVID-19 were approved recently, there is still an important need for additional vaccines to meet global demands.

About the product

COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The coding sequence for the SARS CoV-2 S protein in the vaccine has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS CoV 2 is expressed locally stimulating neutralising antibody and cellular immune responses.

The active substance consists of a recombinant, replication-deficient (E1 and E3 deleted) chimpanzee adenovirus (ChAdOx1) that encodes the SARS-CoV-2 (nCoV-19) spike protein combined with a tissue plasminogen activator (tPA) leader sequence. AZD1222 is propagated in T-REx-293 cells, a derivative of the HEK293 cell line. The expression cassette for the nCoV-19 spike protein fused to the tPA leader uses a modified human cytomegalovirus (CMV) promoter and a bovine growth hormone polyadenylation sequence. The HEK293 cell line is an immortalised cell line of primary human embryonic kidney cells transformed by transfection with sheared human adenovirus serotype 5 (HAdV5). The E1 region (E1A and E1B genes) of HAdV5, is stably integrated into chromosome 19 in HEK293 cells. The expression of the E1 region genes by HEK293 cells and its derivatives e.g. T-REx-293 cell line, allows these cells to be used for the propagation of E1-deleted replication-deficient adenoviruses.

The vaccine is administered intramuscularly (IM) in two doses of 2.5×10^8 infectious units (Inf. U) given between 4 and 12 weeks apart.

Intended indication: *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 use of this vaccine should be in accordance with official recommendations.

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.
- Unmet medical needs will be addressed
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The Applicant provided the following justification with regards to the above criteria: "*the global COVID-19 pandemic causing a health crisis with severe illness, hospitalisations and death in many individuals, as well as major disruption to healthcare systems, it is clear that wide access to multiple effective vaccines is urgently needed. On the basis of the safety and efficacy data generated to date, AZD1222 is anticipated to help fulfil this urgent unmet medical need.*

The benefit-risk profile for AZD1222 in the proposed indication is considered to be positive in adults from 18

years old and above, including older adults above 65 years old and those with comorbidities. Thus, AZD1222 is anticipated to have a significant impact for global populations as well as public health professionals, and will address the urgent unmet medical need in the global health crisis of the ongoing COVID-19 pandemic. Details of the efficacy and safety data in studies conducted with AZD1222 to support conditional marketing authorisation are located within the dossier in Module 2.5. Moreover, the easy storage and handling of the AZD1222 formulation is anticipated to be an important benefit that enables wide access to the vaccine.

The Applicant concludes that the request for a conditional marketing authorisation is duly substantiated for the AZD1222 vaccine for the prevention of COVID 19 in adults".

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a multidose suspension for injection containing ≥ 2.5 × 10^8 Inf.U (infectious units) per 0.5 mL dose, of ChAdOx1-S (recombinant), the adenovirus vector encoding the SARS-CoV-2 spike glycoprotein, as active substance (AS).

Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate (dihydrate) and water for injections.

The product is available in a 5 mL multidose vial presentation (10 doses) in a 10-vial pack and a 4 mL multidose vial presentation (8 doses) in a 10-vial pack. The type I glass vials have an elastomeric stopper with aluminium overseal.

2.2.2. Active substance

General information

The active substance (AS), AZD1222 is a recombinant, replication-deficient (E1 and E3 deleted) chimpanzee adenovirus (ChAdOx1) that encodes the SARS-CoV-2 (nCoV-19) spike protein combined with a tissue plasminogen activator (tPA) leader sequence. AZD1222 is propagated in T-REx-293 cells, a derivative of the HEK293 cell line. The expression cassette for the nCoV-19 spike protein fused to the tPA leader uses a modified human cytomegalovirus (CMV) promoter and a bovine growth hormone polyadenylation sequence. The HEK293 cell line is an immortalised cell line of primary human embryonic kidney cells transformed by transfection with sheared human adenovirus serotype 5 (HAdV5). The E1 region (E1A and E1B genes) of HAdV5, is stably integrated into chromosome 19 in HEK293 cells. The expression of the E1 region genes by HEK293 cells and its derivatives e.g. T-REx-293 cell line, allows these cells to be used for the propagation of E1-deleted replication-deficient adenoviruses.

Adenoviruses such as AZD1222 are non-encapsulated, icosahedral particles (virions) between 80 and 100 nm in diameter. The particles contain a single copy of the double-stranded DNA genome.

The structure of the nCoV-19 spike protein gene construct encoded in the AZD1222 genome is shown in **Figure 1** below.

Figure 1 Structure of the nCOV-19 spike protein gene expression cassette (6214 bp)

Manufacture, process controls and characterisation

The AS manufacturing and testing facilities are described, and the manufacturing sites of the active substance are provided in **Table 1**.

Table 1 AS Manufacturing sites

Henogen S.A. Rue de la Marlette 14 7180 Seneffe Belgium
Catalent Maryland, Inc Main Building (BWI) 7555 Harmans Road Harmans, MD 21077 United States
Oxford Biomedica (UK) Limited Unit A Plot 7000 Alec Issigonis Way Oxford OX4 2ZY United Kingdom

A major objection was raised for the certificate of GMP compliance for the Catalent site in the USA. The certification has now been issued and the major objection resolved. Appropriate GMP certificates for all sites are available. Although defined supply chains are proposed, the applicant may use AS manufactured at any site approved in the MA to manufacture AS at any FP site approved in the MA.

The manufacturing process is divided into cell culture and downstream processing.

The cell culture consists of four steps: vial thaw, inoculum expansion in shake flasks and rocker bags, seeding of bioreactor(s) for further expansion of inoculum and production bioreactor to generate crude AZD1222. For the description of the manufacturing process, the process parameters (critical process parameters (CPPs) and non-critical process parameters NCPPs), process outputs (in-process controls (IPCs), microbial controls (MCs) and performance attributes (PAs) are considered satisfactory.

The production bioreactor cell culture is lysed using detergent-based cell lysis, treated with nuclease for reduction of host cell DNA and then clarified via depth filtration. The clarified lysate is further processed

through a membrane chromatography step designed to remove process-related impurities. This is followed by concentration and diafiltration using tangential flow ultrafiltration to remove process-related impurities and for buffer exchange. Next, a formulation step and a 0.2 µm filtration step into specified containers follows to generate the AS. The AS is frozen for storage (at -90°C to -55°C) and shipping.

The description of the downstream manufacturing process steps (Steps 5-11) is considered acceptable. For each step, the critical process parameters (CPPs) and non-critical process parameters (NCPPs) with their acceptable ranges, the IPCs with their acceptance criterion and the PAs with their action limits are listed. In the production bioreactor step the multiplicity of infection (MoI) is considered an NCPP. After all validation efforts are completed, all process parameters (including MoI), their acceptance ranges and criticality will be reviewed (recommendation). Several safety tests are included as IPCs, including tests for absence of replication competent adenoviruses (RCA). For the RCA assay no validation data had been provided. This was considered a Major Objection. In the response, the applicant has submitted the validation report as requested. In this regard, the Major Objection was considered solved, although several points for clarification were still raised regarding the possible interference of the test article with replication of low amounts of Adenovirus 5. Upon request, acceptance criteria for sample and system suitability of the method were set for both RCA testing sites. With regards to the *in vivo* assay for adventitious agents, the applicant requested removal of the test and this was considered acceptable and in line with regulatory 3R considerations (replacement, reduction and refinement with respect to animal testing).

Further minor clarifications were requested regarding the manufacturing process and control, which have been provided.

Specific reprocessing conditions are justified. Column and membrane sanitisation and re-use is described.

The batch definition and numbering system is provided for the different AS manufacturing sites.

Control of materials

A list of all raw materials used in manufacturing of AS, cell banks and virus seeds are provided in this section. According to the applicant, the raw materials are purchased from quality-approved suppliers according to approved procedures. Materials are inspected upon receipt and supplier certificates of analysis are reviewed. These raw materials are tested and released according to approved specifications (in-house or compendial as relevant). Specification changes follow quality change control procedures prior to implementation. The supplier of culture media used will inform the applicant of any changes in their composition. The applicant also confirmed that no material of human or animal origin are used in the growth medium or feed (including no materials manufactured with animal-derived material). No materials of human origin other than the T-REx-293 cells themselves were used in the host cell line culture, virus seed development, preparation of the host cell banks and AZD1222 virus seeds, or AS manufacturing process.

Several materials of animal or other biological origin are used in the current manufacturing process and were used in the development and manufacture of the cell banks and the virus seeds. Nuclease is the only raw material of animal origin used in the AZD1222 manufacturing process. One specified material of animal origin was used in the preparation of cell banks and virus seed banks. Several materials of animal origin were used in the development of vector construct and pre-GMP cell bank. Reference is made to the Adventitious agents section for detailed information. Certificates of analysis and/or certificates of origin as well as certificates of suitability with regards to TSE (when relevant) are included.

The AZD1222 recombinant adenovirus is propagated and manufactured using the T-REx-293 host cell line which was derived from a HEK293 cell line. The AZD1222 virus is replication-defective by deletion of the E1

gene. The T-REX-293 cells provide the E1 genes in trans, enabling replication of the replication-defective AZD1222 virus. The T-REx-293 cell line has been engineered to stably express the tetracycline (Tet) repressor protein. In the absence of tetracycline, the Tet repressor protein represses transcription of the SARS-CoV-2 S-protein in order to increase viral yield. A map of the plasmid that was used for construction of the T-REX-293 cell line as well as details of the genetic elements has been provided.

The production cell line T-REx-293 was acquired to generate a development Master Host Cell Bank (MHCB). This development MHCB was used to generate a pre-GMP Virus Seed material from which a research virus seed was later manufactured and tested.

The cell banking systems has been briefly but appropriately described. The cell banking system is a tiered system including a MHCB from which a working host cell bank (WHCB) Lot was produced.

The MHCB and WHCBs have been tested for identity, sterility, mycoplasma, mycobacteria, electron microscopy, retroviruses and adventitious agents by in vivo and in vitro methods, in line with Ph. Eur. 5.2.3 and ICH Guideline Q5D. Although the testing is generally considered acceptable, further clarification for the testing panel for adventitious viruses was requested because there are tests only performed in some of the banks and sometimes alternative tests are used for different banks without further explanation. A more detailed justification for the testing approach was provided and is considered acceptable. Also, a viral risk assessment was requested in order to justify that the proposed virus testing in animals on future WHCBs is really needed, contributing to the risk mitigation taking into account the overall testing package. The applicant justified that this animal testing is based on the global development since some parts of the world request these tests. For the WHCBs and future WHCBs, an identity test was requested that is able to identify T-Rex cells. The further justification presented by the applicant was found acceptable, i.e. the current identity test is considered sufficient. Future WHCBs will be manufactured following the same process as the existing AstraZeneca WHCBs.

Brief but sufficient information has been presented to understand the steps followed to generate the AZD1222 recombinant adenovirus vector. The vector itself (ChAdOx1) was derived from the chimpanzee adenovirus Y25 that was rendered replication-deficient by the deletion of the E1 gene. Other modifications include the deletion of the E3 gene and the substitution open reading frames for those from human adenovirus serotype 5. The nucleotide sequence encoding the recombinant S protein was codon optimised to improve expression in human cells. DNA encoding the tissue plasminogen activator (tPA) signal sequence was fused upstream of the S protein coding sequence. The bovine growth hormone (bGH) polyadenylation signal is located downstream of the S protein coding sequence. Transcription of the S protein gene is driven by a tetracycline-regulated long CMV (LPTOS) promoter that contains operator binding sites for the Tet repressor protein. The transcription of the S protein gene is inhibited when the Tet repressor protein is present, as during the production of the adenovirus in T-REx-293 cells, thereby enhancing production.

The construction of the plasmid p5713 pDEST-ChAdOx1-nCOV-19 has been well described. Furthermore, the nucleotide and amino acid sequence of the SARS CoV-2 S protein gene containing the tPA leader sequence has been provided. It is noted that the coding sequence for the SARS CoV-2 S protein in the vaccine has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. The preparation of the research virus seed (RVS) is suitably described. The RVS was tested for mycoplasma, endotoxin, bioburden and infectivity.

The virus seed system employed for AZD1222 is a tiered system including a master virus seed (MVS) from which working virus seeds (WVS) are generated. An initial MVS was produced and was exhausted therefore a

new MVS was produced. From this new MVS, four WVS were produced, one of them further re-aliquoted into four sublots.

MVS and WVS have been tested for identity, bioburden, endotoxin, mycoplasma and mycobacteria, and adventitious viruses. Genetic stability of the MVS and WVS is investigated. Results are acceptable and showed there were no changes detected within the viral genome and the viral genome matched the predicted sequence. The protocol and panel of tests that is proposed for qualifying a new WVS is acceptable.

Given the additional in-process controls of adventitious viruses performed on every batch manufactured, the approach can be considered acceptable.

Also, for the virus seeds a viral risk assessment was requested in order to justify that the proposed virus testing in animals for future WVSs contributes to the risk mitigation, taking into account the overall testing package. This issue was adequately addressed (see above for WHCBs).

Control of critical steps and intermediates

Bioburden and endotoxin action limits for process intermediates and some process solutions are provided and are considered acceptable.

Hold times for AS process intermediates are validated though a combination of a small-scale study of biochemical hold stability and a commercial scale study demonstrating effective microbial control during the hold times. The hold times are currently being validated and the expected maximum hold times based on biochemical hold stability (based on development data) are provided. However, the small-scale and the commercial scale validation studies have not been completed. The applicant is requested to include the analytical results of both studies for assessment post-authorisation (recommendation). After completion of the hold time studies the applicant is requested to assess the combined impact of all holds on the cumulative decrease in infectivity during the hold times (recommendation).

The removal of some of the process-related impurities is measured in several downstream intermediates without acceptance criteria or action limits. Given the proposed concurrent validation strategy, it was requested that for several impurities (e.g. residual host cell DNA, residual host cell protein (HCP), residual nuclease) that action limits are proposed in the validation protocols. The applicant indicated that setting action or acceptance limits would be premature because pre-PPQ lots are used to identify these limits. The explanation is accepted. With the concurrent validation proposal, process removal of some of the impurities is still being validated. Introduction of action limits in the validation protocols would be appropriate. However, given that testing of most of the impurities are included in the AS specification during validation, this approach is accepted.

The NCPPs can only be considered non-critical within the ranges tested. The applicant indicated that NCPPs are also monitored during validation studies and that after sufficient manufacturing experience has been obtained, the parameters of the control strategy will be reviewed (recommendation).

Process validation

The strategy for process validation for AZD122 AS includes three stages:

- *Stage 1-Process Design:* The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- *Stage 2-Process Qualification (Validation*): The process design is evaluated during this stage to determine if the process is capable of reproducible commercial manufacturing.

- *Stage 3-Continued Process Verification*: To gain assurance during routine production that the process remains in a state of control.

Currently available process validation data available for all the process steps are provided. Tables listing available data are presented that include CPPs; NCPPs; IPCs; MCs; and PAs. The applicant has provided validation data of batches manufactured at all facilities and of one additional supporting batch manufactured at a site not included in the current application dossier but used to manufacture full scale process material.

Validation has not been completed. Validation protocols are provided where available. Protocols for the manufacturing process at Catalent Maryland, Henogen S.A., and Oxford Biomedica are presented. Furthermore, protocols for additional validation activities have been provided that include intermediate hold validation, cleaning validation, filter validation, AS shipping qualification and reprocessing validation. In the absence of complete validation data, available process performance data are provided from individual lots, including lots manufactured prior to process validation but using the same process, scale and manufactured in the same facilities as the validation lots. Additional data have been provided for Catalent Maryland, Inc., Henogen S.A. and Oxford Biomedica (UK) Limited manufacturing sites, although some results are not yet available. The applicant should provide additional data to complete manufacturing process validation (Specific obligation 1).

A tangential flow filtration (TFF) membrane lifetime and carryover study will be performed. An appropriate cleaning validation protocol for TFF membrane lifetime, carry over and storage was provided. Since these data are being generated currently and will be used to inform future re-use, the data may be provided post-authorisation (recommendation). Based on the provided risk assessment it can also be agreed that leachables from the different materials used in the AS manufacturing process pose a minimal safety risk.

Appropriate studies were performed to validate the use of the 0.2 µm filters for filtration of the AS bulk. The shipping performance qualification is considered sufficient to qualify the general shipping process to be able to maintain the temperature between -55°C and -90°C and ensuring container integrity. Some study results are awaited regarding shipping (recommendation). The maximum time the material can be exposed to ambient temperatures during normal shipping and receiving processes (to assure that the material remains frozen, integral and acceptable for the intended use) was studied in thermal-cycling experiments.

Formulated bulk may be reprocessed. The validation report from the small-scale study and the full-scale site-specific protocols should be provided post-authorisation (recommendation).

For several parameters, the applicant refers to the corresponding protocol for the acceptance criterion or action limit. The applicant is requested to provide in a table, the acceptance criteria or action limit for all parameters tested and if they differ between the various facilities (recommendation). The applicant should submit an updated manufacturing process validation section, including the data requested when validation is completed (recommendation).

The control strategy employed during process validation includes monitoring of performance output parameters which are not IPCs and acceptance criteria for NCPP. This should be maintained until sufficient validation data have been obtained and the non-criticality of NCPP has been demonstrated. The proposed acceptable range for several CPPs is rather wide. After completion of the validation of the commercial process at three commercial sites, the applicant should review all CPPs and also the status of the NCPPs based on comprehensive validation data (recommendation).

At submission, complete validation data was missing from all manufacturing sites. This was considered a Major Objection. In the applicant’s response, more validation data for Catalent, Oxford Biomedica and

Henogen were submitted (see also manufacturing process development section. These data demonstrate process consistency and quality sufficient to support approval of a conditional marketing authorisation for this product although pending data from each of the three sites is requested post-approval to complete the validation data (Specific obligation 1).

Manufacturing process development

Critical Quality Attributes (CQAs) are identified by conducting a risk assessment to evaluate the potential impact of the quality attributes on the safety and efficacy of the product. As defined in ICH Q8(R2), the goal of the control strategy is to ensure critical quality attributes of AS and FP are within the acceptable ranges. Various elements of the control strategy are outlined and the CQAs that are affected by CPPs are defined. Characterisation of product and process related impurities are also described. An overview of the analytical testing controls is provided and the commercial control strategy for each quality attribute is summarised. Finally, process characterisation studies were conducted to determine the effects of manufacturing process parameters on product quality and process performance were assessed, leading to identification of critical process parameters.

Four manufacturing processes were used during the development of AZD1222: Process 1 (nonclinical toxicology and initial clinical manufacturing), Processes 2 and 3 (clinical manufacturing), and Process 4 (commercial manufacturing).

Two comparability exercises have been performed to demonstrate comparability between AS batches used in clinical studies (Processes 1, 2 and 3) and between AS clinical batches and the commercial manufacturing process (Process 4).

To demonstrate that AS clinical processes (Processes 1, 2 and 3) are comparable, a combination of all batch release and characterisation tests. The applicant concludes that results from comparative testing for these lots demonstrates the analytical comparability between AZD1222 Process 1, Process 2, and Process 3 AS. This conclusion is endorsed. Some minor points were further clarified upon request.

The comparability between clinical manufacturing processes and commercial Process 4 has been evaluated using batch release and characterisation results and degradation trends of AS manufactured by Process 3 and 4 at accelerated stability conditions. The tests performed in the comparability analysis are acceptable, however, the acceptance ranges for several attributes were considered too wide and were requested to be tightened to ensure comparability between commercial and clinical batches. This was considered a Major Objection. In the response, the applicant explained that given the limited manufacturing experience, the prediction interval approach has been followed to inform the comparability ranges. The justification presented by the applicant is considered acceptable, but the acceptance ranges should be revised when more manufacturing experience is available (recommendation).

Release and characterisation data have been provided from a suitable number of commercial scale PPQ and/ or Pre-PPQ batches manufactured by Process 4 at the commercial manufacturing sites. Although data are not complete in all cases, they are considered sufficient.

Regarding the accelerated stability degradation rates, data from a suitable number of batches manufactured by the clinical Process 3 at a non-commercial site are provided. Data are used to compare the clinical batches with the commercial Process 4 batches.

Some supporting Process 4 batch data from another site are also available. This site is not included as manufacturing site. Complete results are provided. Degradation rates are comparable to Process 3.

Regarding the commercial AS manufacturing sites, from the pre-PPQ/PPQ data submitted degradation rates are comparable to Process 3.

The applicant states that all available lot release, characterisation and stability test results from the AS comparability studies meet the pre-defined comparability assessment criteria and demonstrate that AZD1222 Process 4 AS is comparable to Process 1, 2, 3 AS.

This conclusion had not been fully supported during initial assessment since it could not be concluded that AZD1222 Process 4 AS is comparable to Process 1, 2, 3 AS for all three AS sites until further results were evaluated. This was considered a Major Objection. In the submitted response, the applicant provided further comparability data (results detailed above are current) for Catalent, Oxford Biomedica and Henogen. For this conditional marketing authorisation, these data sufficiently demonstrate comparability of AS manufactured at these sites to AS used to formulate product used in clinical studies. However, completion of the comparability data package is still requested and further data are requested after approval (Specific obligation 1).

Characterisation

The structural characteristics of AZD1222 have been examined using orthogonal analytical methods to analyse the biological activity; structure/identity; morphology; size heterogeneity; molar mass; and particulate matter.

A reference standard (RS) is employed in two release tests. The two reference standard batches manufactured to date were analysed in the characterisation studies (one from process 3 and another one from Process 4). Different virus and cell banks were used to produce both RSs. Of the characterisation tests, the same tests were not used to characterise both RSs. This testing is however complementary and although it is considered sufficient for authorisation in this case, complete characterisation should be performed at least with one GMP AS batch manufactured using the commercial Process 4 (recommendation).

Regarding the product-related impurities that may be present in AZD1222 AS and/or FP empty viral particles, non-infective viral particles and aggregates are suitably controlled. These are the most important identified product-related impurities. In addition, it is sufficiently demonstrated that AZD1222 has a low tendency to aggregate and multiple process, formulation and analytical testing control elements are in place to ensure minimal aggregation levels in AZD1222.

Process-related impurities are identified. Results of AS levels of host cell DNA, host cell protein and nuclease are presented for the process 1-3 clinical and Process 4 commercial lots. All results are well within the currently proposed acceptance criteria. Host cell DNA, host cell protein and residual nuclease used in AS purification will however be controlled via AS release testing.

A risk assessment was performed to evaluate the other impurities. This is acceptable.

Small molecules and synthetic macromolecules include process-related impurities and some medium and buffer components. Impurities in this group are evaluated through an alternative safety risk assessment based on quantitative toxicity data. All small molecule and synthetic macromolecule process-related impurities used in the manufacturing process present minimal safety risk based on the risk assessment results.

All specified impurities have been present in product used in clinical trials. Some other minor issues were raised regarding characterisation and adequately addressed. The testing panel is considered acceptable.

Specification

The AS is tested for the general tests of appearance, color, pH, osmolality, and polysorbate 80. The potency tests of infectivity and the purity tests of DNA to protein ratio and viral particle to infectivity ratio. Also performed are identity by qPCR, viral particle concertation by anion exchange chromatography, impurities by residual DNA, Host Cell Protein, and nuclease, and the safety tests of bioburden and endotoxin.

The tests used for AS release are acceptable but were not considered complete. In addition to the infectivity potency test, a potency test which measures the transgene expression is considered important and was requested to be included (Major objection). In the response, the applicant explained that the test used in characterisation studies is being further developed to make it suitable for QC testing and subsequent introduction into the MA post-approval. Whilst the test is required to be introduced for release for AS, the method to determine transgene expression may be semi-quantitative/ qualitative. The applicant should validate and implement the method for transgene expression for all AS and FP sites (recommendation). The major objection is considered solved.

In addition, absence of RCA is evaluated as IPC in the AS bulk harvest which is acceptable. This had been raised as a Major Objection which is now solved, because the applicant agreed to add the absence of RCA (by IPC) as a footnote to the AS Specification.

Acceptance criteria established for safety, concentration and impurities assays were requested to be reviewed/tightened because they were not considered representative of the analytical results of the AS batches manufactured by clinical processes. All these issues were considered a Major Objection. In the submitted response, the applicant agreed to tighten several acceptance criteria at both AS and FP level. Upon request the HCP acceptance criterion has been further tightened to an acceptable level. The infectivity specification has been increased to maintain alignment with the revised FP specification.

The proposal from the applicant to tighten certain specification limits is acceptable. The acceptance ranges should be reviewed when more manufacturing experience is available (recommendation). Specifications will be updated in the dossier. The major objection is considered solved.

Analytical methods

Validation reports were in accordance with ICH guidelines and demonstrate the suitability of the non-compendial analytical methods used for lot release and stability testing of AS (and FP when appropriate). Validation reports are provided for several sites. For some methods, validation has been performed by AZ and co-validation is presented for additional testing sites. For other methods, method transfer reports are provided. The reports provided are acceptable. The methods used in each manufacturing site were indicated, however validation of analytical procedures is not complete. Some method-transfer or method validation is still ongoing, and reports will be provided in February 2021 (recommendation). AZ confirmed that that the release testing at QC sites will only occur once the method transfer or method validation is successfully completed.

Method descriptions are very concise and for some, additional information was requested.

For infectivity, residual nuclease, host cell DNA and host cell protein, two versions of the method description are provided. As different methods will be used for release at different sites, a method comparison should be performed to demonstrate that these methods generate comparable results (recommendation). The suitability of the HCP assay has been assessed by demonstrating the coverage of the HCPs representative of the manufacturing process with the T-REx cell line.

Key potency / content tests are described below.

Viral particle concentration by AEX: Anion Exchange-High Performance Liquid Chromatography (AEX-HPLC) is used in combination with an absorbance ratio to determine the concentration of viral particles.

Infectivity: the infectious titer of Drug Substance and Drug Product is determined using a cell-based infectivity assay. AZD1222 Infected HEK283 cells are immuno-stained and enumerated by light microscopy.

Batch analysis

In summary, the release data presented of AS batches manufactured by commercial Process 4 at the different manufacturing sites all at commercial scale are provided. Data from a suitable number of Pre-PPQ and PPQ lots are provided.

The absence of complete release and comparability data from all AS sites applied for in the MAA had been raised as a Major Objection. In the response, the applicant sent more release data for Catalent, Oxford Biomedica and Henogen. The data presented demonstrate sufficient process consistency, quality and comparability to AS used to manufacture clinical FP lots. This supports approval of a conditional marketing authorisation although pending data from each of the three sites is requested post-approval to complete the validation data (Specific obligation 1).

Reference materials

A Reference Standard (RS) is used for specified tests. Two reference standards have been manufactured to date.

An RS should be established from a GMP batch of AS manufactured by commercial Process 4. This was raised as a Major Objection. In the response, the applicant clarified that the AS batch from which the current RS was established has been manufactured at a commercial manufacturing site, at commercial scale and following the commercial manufacturing process. This is acceptable and the MO is considered resolved.

The Applicant should include at a minimum, tests to analyse virus identity, virus protein fingerprint, transgene expression and level of aggregates in the RS qualification protocol; and should also qualify future RSs using previous RSs. Stability/trending criteria should be set to monitor the stability of the RS (recommendation).

Container closure system

The applicant has used two types of primary container closure systems for the AS storage.

The description of both containers and the materials of construction are provided in the dossier. Materials of construction are compliant with Ph. Eur. Both containers are pre-sterilised by the vendor using gamma irradiation.

The suitability of both containers has been assessed with regards to 1) protection of the AS from environmental exposure, 2) safety of the container components, 3) compatibility of the AS with the container and 4) performance of the container. For both containers, protection has been demonstrated by the vendor with tests compliant with Ph. Eur. Safety has also been demonstrated by physicochemical/biological reactivity tests and by extractables/leachables studies performed by the vendor in accordance with Ph. Eur. 3.1.5, USP<661>, USP<87>, USP<88>.

In addition, the applicant has performed a forced-degradation study for each type of container to monitor the compounds most likely to leach from the container components, including volatile compounds, semi-volatile

compounds, non-volatile compounds and elements. The applicant has committed to carry out a simulation leachables study to monitor the compounds identified. The conditions of these studies are included in the dossier and results will be available in March 2021. This information should be provided post-approval (recommendation).

For both types of containers, the applicant demonstrates compatibility of the container with the AS by the results of stability studies provided in section S.7. Validation was also evaluated by the vendor for both containers.

Stability

A shelf life of 6 months at -90 to -55°C is proposed for the active substance.

Stability studies are in progress to establish the AS shelf life at the long-term storage condition of -90 to -55°C following ICH Q5C.

In addition, studies to evaluate the stability of the product at 2-8°C, 23-27°C /55-65% RH and after 3X freeze-thaw cycles are ongoing. These stability studies include batches manufactured by process 3 (clinical, Cobra) and by process 4 (engineering, pre-PPQ and PPQ, manufactured at Oxford, a site not intended for commercial manufacture of AS for this product, Catalent and Henogen).

For these studies, the batches are stored in either of the containers specified for commercial use. The commercial formulation was used to manufacture all lots. The parameters analysed are suitable for stability testing. The acceptance criteria for these parameters are identical for release and for stability.

Data from lots manufactured by Process 3 at a site not intended for commercial manufacture of AS for this product are available following storage under real-time and accelerated conditions.

Limited stability data are available for the commercial batches.

Considering the pandemic scenario and this conditional marketing authorisation, the Process 3 stability data can be considered sufficiently representative for commercial product to permit approval of a product shelf life. However, additional stability data are required to confirm this (Specific obligation 2) A shelf life of 6 months at -90 to -55°C for the AS is approvable based on data obtained from batches manufactured. The applicant should submit a variation to extend the shelf-life, supported by real time data (recommendation).

In addition, additional data demonstrating comparability between process 3 and process 4 batches should be provided (see AS manufacturing process development section) (Specific obligation 1). The post-approval stability protocol included in the dossier is found adequate. Any confirmed out-of-specification result, or significant negative trend of ongoing stability studies, should be reported to the Rapporteur and EMA.

A shelf life of 6 months at -90 to -55°C for the AS is agreed.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a liquid dosage form intended as an unpreserved multiple-dose vial for administration by intramuscular injection. There are two FP presentations containing either 8 doses or 10 doses per vial, 0.5

mL per dose, as described in Table 2. The 5 ml presentation is available in two configurations of a 6 mL or 10mL vial. The FP primary packaging comprises clear and colourless vials, closed with elastomeric stoppers and sealed with aluminium overseals. The FP (10 vials) is packaged in a carton.

Table 2: Intended Commercial FP presentations

Number of Doses/Vial	Drug Product Manufacturer	Label-Claim Volume	Overfill Volume	Target Fill Volume	Vial Size	Stopper and Overseal Size
8	CP Pharmaceuticals Limited	4 mL	1.1 mL	5.1 mL	5 mL	13 mm
10	IDT Biologika	5 mL	1.45 mL	6.45 mL	6 mL	20 mm
10	Catalent Anagni	5 mL	1.5 mL	6.5 mL	10R	20 mm

The FP formulation is identical for the two presentations. Excipients are well known and compliant to Ph. Eur. and include: L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, magnesium chloride hexahydrate, disodium edetate dihydrate (ethylenediaminetetraacetic acid, EDTA), sucrose, ethanol, polysorbate 80 and water for injections. L-histidine and L-histidine hydrochloride monohydrate provide buffering, Sodium chloride and sucrose act as tonicifier/stabilizer, magnesium chloride hexahydrate and disodium edetate dihydrate (ethylenediaminetetraacetic acid, EDTA) act as a stabilizer. All excipients meet regional compendial requirements. There are no novel excipients used in the finished product formulation. Each 0.5 mL dose contains ≥ 2.5×10^8 Inf.U (infectious units) per 0.5 mL dose of AZD1222. The applicant initially proposed to express the strength (potency) of AZD1222 as viral particles/ml on the label. However, for clinical efficacy the number of infectious viruses are of prime importance and currently licensed live viral vaccines and recombinant viral vectored are labelled in infectious units. The applicant has updated the finished product composition label to include the minimum number of infectious viruses instead of viral particles as the descriptor for strength.

To meet injection and extractable volume requirements, the FP is filled with a volume in excess of the label-claim volume. The excess (or overfill) volume accounts for product losses from hold-up volumes experienced during product withdrawal from the vial and administration using a syringe and needle (see Table 2) and was justified by a study. The FP does not contain an overage. The company should study whether it is possible to withdraw more than 8/10 doses from the respective vials using low dead-volume syringes. (recommendation).

Based on product knowledge and scientific understanding, the formulation parameters which were considered to have a relatively high risk of impacting CQAs and interacting with other formulation parameters were evaluated.

The FP was developed to be stable for at least 6 months at the intended long-term storage condition of 2-8°C. No additional work was done to develop a formulation containing a preservative, which is acceptable in view of the urgent need for COVID-19 vaccines.

A number of univariate and one multivariate formulation characterisation studies were conducted to evaluate the stability and robustness of the formulation. These studies are still ongoing and the applicant should submit the results of the formulation robustness studies when they are finalised (recommendation).

Manufacturing Process Development

Changes that have been included in the FP during process development have been described. Three FP manufacturing processes have been used during clinical development. The main changes of the processes are dosage form, FP storage condition, label claim/fill volume, type of container closure system and manufacturing sites.

The comparability assessment includes process comparison as well as analytical comparability studies. The analytical comparability studies comprised all batch release tests and additional characterisation tests. Data have been provided.

Differences in strength related attributes between final product batches manufactured according to process 1, 2 and 3 are present. The clinical doses, by taking into account the corresponding dosing volume of each FP lot, are however comparable. The applicant concludes that results from this comparative testing demonstrate the analytical comparability between AZD1222 Process 1, Process 2, and Process 3 FP. This conclusion is endorsed.

A comparability assessment has been performed following a pre-approved protocol to demonstrate that the clinical processes are comparable to the intended commercial process 4. The analytical assessment comprises all commercial batch release tests and some characterisation assays. The batch release specification and prediction interval of the attribute levels from clinical processes have been set as part of the comparability acceptance criteria. However, prediction intervals were considered unsuitable for determining comparability ranges; the prediction intervals result in broad comparability intervals. This was considered a Major Objection. In the response, the applicant presented additional justification for the establishment of the comparability ranges. If the test is directly linked to clinical performance, uses the specification method and/or considered to be the main test for related attributes, the prediction interval is tightened. The justification and revised comparability testing plan presented by the applicant is considered acceptable, but the ranges should be revised when more manufacturing experience is available (recommendation).

With the comparability data provided at submission, comparability could not be demonstrated between clinical processes and Catalent Anagni as no batch data were provided. Similarly, it was not possible to assess the comparability between clinical processes and the batch manufactured at CP Pharmaceuticals, as critical quality attribute data were still pending. This was considered a Major Objection. In the submitted response, the applicant provided a substantial amount of additional comparability data for Catalent Anagni, IDT Biologika and CP Pharmaceuticals. For this conditional marketing authorisation, these sufficiently demonstrate comparability of FP manufactured at these sites to FP used in clinical studies. However, completion of the comparability data package is still requested and further data are requested after approval (Specific obligation 1).

A process risk assessment was employed to facilitate overall process risk management for the FP manufacturing process. The risk assessment was informed by prior knowledge from scientific understanding, earlier clinical manufacturing and characterisation studies. Three categories of process characterisation activities have been performed such as characterisation of process steps (process parameters risk assessment, characterisation studies and critical process parameter determination), quality impact of the manufacturing environment (environmental factor risk assessment, CQA impact study and process control implementation) and in-process leachables (questionnaire-based evaluation, detailed risk assessment and safety assessment). The overall strategy followed to characterise the FP manufacturing process is supported.

The microbiological attributes of the dosage form have been discussed. The FP is intended for multiple doses but does not contain a preservative, and therefore, antimicrobial preservative effectiveness testing was not

performed. The FP is intended to be used within a limited in-use period, specifically a maximum of 48 hours at 2-8 ° C and within this period up to 6 hours at 30 °C (after a 30 °C storage, the product must be used or discarded). Microbial challenge studies were designed and executed to support the maximum intended in-use times for the FP. However, results of microbiological challenge would not be considered as representative for real-life conditions of use and the requirement for labelling according to the Note for guidance on maximum shelf-life for sterile products for human use after first opening or following reconstitution, for unpreserved sterile products (CPMP/QWP/159/96 corr) should be followed i.e. from a microbiological point of view, after first opening the vaccine should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

The in-use compatibility study was designed to evaluate biochemical stability of the FP 1) with syringes and needles; and 2) for the last dose remaining in a 10-dose vial in the event that this last 0.5 mL is held in the vial beyond the maximum allowable in-use times in a worst case scenario. For this study, in-use compatibility of Process 4 FP was assessed using sterile 1 mL polypropylene and polycarbonate syringes with a 25-gauge, 1.5-inch needle. Agitation, hold temperatures/times and light exposure were combined into one study to provide a cumulative set of worst-case conditions. The product quality and stability results from the biochemical compatibility studies demonstrate that the FP is compatible with clinical administration components, dose preparation procedures and in-use conditions (agitation, temperature, and light) including for multiple dose withdrawals. In conclusion, the results of the biochemical compatibility study support the use of the FP by intramuscular injection and for in-use times of 48 hours at 2 – 8°C or 6 hours at room temperatures up to 30°C for a single period within this time (refer to the FP stability section for the precise 'in-use' approved instructions after opening the vial). As indicated in the CHMP note for guidance on in-use stability testing of human medicinal products, results of at least two batches should be presented to support the in-use physical-chemical stability. It is recommended that the applicant performs in-use stability testing using an additional FP batch, which is towards the end of its shelf-life to confirm these data (recommendation).

Manufacture of the product and process controls

Manufacturer

The FP manufacturing facilities are provided in Table 3. During the procedure a major objection was raised on some sites to seek appropriate GMP certificates to conduct the proposed functions. This was resolved and all the manufacturing and testing sites now have appropriate GMP certificates.

Table 3: FP manufacturing sites

Catalent Anagni S.R.L. Località Fontana del Ceraso S.P. Casilina, 41 03012 Anagni (FR) Italy
CP Pharmaceuticals Limited Ash Road North Wrexham LL13 9UF United Kingdom

IDT Biologika GmbH
Am Pharmapark,
Dessau-Rosslau 06861 Sachsen-Anhalt,
Germany

MedImmune Pharma BV, Nijmegen, The Netherlands site performs EU batch release.

Description of manufacturing process and process controls

The applicant has presented the description of the manufacturing process and process control for the three intended manufacturer sites in EU, which are Catalent Anagni (Italy), CP Pharmaceuticals (Wrexham, UK) and IDT Biologika (Dessau-Rosslau, Germany). A similar manufacturing process is used at the three manufacturing sites.

A process flow diagram summarising the manufacturing process, as well as the material inputs, critical and non-critical process parameters, and process outputs (in-process controls and performance attributes) is provided for each FP manufacturing site.

The frozen AS is shipped at -90 to -55°C to the FP fill facility. Upon receipt, the AS is stored at -90 to -55°C prior to processing. The AS is thawed, mixed and pooled into a mixing vessel and dilution buffer is then added to the mixing vessel. Dilution buffer and AS is then mixed to produce final bulk. The final bulk is 0.45 µm (bioburden reduction) filtered into a holding bag prior to filling. During the filling process, the final bulk is 0.2 µm sterile filtered, using redundant sterile filters in series, as it is aseptically filled into sterile vials, closed with sterile stoppers, and sealed with aluminium caps. The resulting FP is 100% visually inspected, packaged and labelled on site.

The following prospective validation studies have been provided for each manufacturing site: validation of sterilisation methods, media fills (to include evaluation of maximum filling time), container closure integrity qualification, filter validation studies, bulk shipment qualification and simulated shipping validation of finished product to secondary packaging/distribution sites. Some of the studies are still on-going and the applicant should provide the completed study reports post approval (recommendation).

PPQ validation protocols for the three manufacturing sites have been provided.

In summary, a minimum of three consecutive, successful process validation lots are being produced. Monitoring of CPPs during validation include assessment against acceptance criteria. IPCs will be included for evaluation during process validation with validation acceptance criteria. NCPPs will be monitored to ensure they are within the specified ranges but not assessed against acceptance criteria during process validation. A hold time period of the formulated bulk will be performed on all three batches, with a target hold time of ≤ 72 hours and at least 48 hours. The FP PPQ activities are ongoing in the three manufacturing sites. Validation acceptance criteria for all CPPs and IPCs have been met for all the batches completed to date. A summary of the batches manufactured at every manufacturing site has been provided.

The applicant has committed to provide the results of the process hold studies, validation of labelling and secondary packaging at commercial scale when available (recommendation).

The applicant should provide the final results for the additional FP in process testing performed as part of the process validation specifically at Catalent Anagni and CP Pharmaceuticals, to ensure that these critical steps in the manufacturing process of the finished product are properly validated as part of the process performance qualification (Specific obligation 1).

The currently available set of validation data for the commercial process at the different sites, although not complete, are reassuring. All results of performance outputs are within acceptance criteria and also the process parameters remain within their acceptance criteria or range. Batch analysis data for CP Pharmaceuticals and Catalent Anagni demonstrating that these sites are able to manufacture FP according to the commercial specifications were initially lacking. In addition, comparability data were not available for product from these sites. Therefore, as requested in the pharmaceutical development section, the applicant was requested to submit the missing batch analysis and comparability data or withdraw CP Pharmaceutical and Catalent Anagni as EU FP manufacturing sites. This was considered a Major Objection. In the response, the applicant submitted more validation and batch analysis data for the three sites. The data presented demonstrate process consistency, quality and comparability to clinical FP, sufficient to support approval of a conditional marketing authorisation for this product although pending data from each of the sites is requested post-approval to complete the validation data (Specific obligation 1).

Container closure system

A description of the container closure system has been provided for the three proposed manufactured sites in Europe. Due to vial shortage the applicant has presented different container closure systems for every manufacturing site. All vials comply with Ph. Eur. 3.2.1. for type I borosilicate glass. The stoppers are manufactured from elastomer, which complies with Ph. Eur. 3.2.9. Sterilisation of container-closure component occurs at the respective site and is adequately described.

As part of the description, the applicant has included identity of materials of construction of each primary packaging component, its specification and drawing of each of the components.

A brief description of the non-functional secondary packaging has been included.

The suitability of the container closure system used for the storage, transportation and use of the FP has been discussed, including the choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction. It was demonstrated that stoppers meet the Ph Eur. 3.2.9. compendial requirements for penetrability, fragmentation and self-sealing. The applicant has committed to provide the results of the leachable safety studies of the container closure system. These results should be submitted post-approval (recommendation).

The applicant has committed to perform a confirmatory photostability study in accordance of ICH Q1B on at least one lot of AZD1222 FP to demonstrate that the design of the FP container/closure in secondary packaging protects the product from potential light exposure during product storage and transportation activities. This should be submitted post-approval (recommendation).

Overall, the level of information provided is deemed acceptable.

Product specification

The FP is tested for the general tests of appearance, color, clarity, visible particles pH, and polysorbate 80, extractable volume, sub visible particles, and osmolality. The potency tests of infectivity and the purity tests of DNA to protein ratio and viral particle to infectivity ratio. Also performed are identity by qPCR, viral particle concentration by anion exchange chromatography, and the safety tests of sterility, container closer integrity testing and endotoxin.

The FP specification is aligned with ICH Q6B and covers the main product characteristics such as physicochemical properties, identity, purity/impurities, content, biological activity and microbiological tests.

Transgene expression (raised as a Major objection) and level of aggregates were requested to be added as FP batch release tests. Based on additional data and justifications provided, it was agreed that there was no need to include a test for aggregates in the specifications. As requested for the active substance, the applicant should develop a semi-quantitative or qualitative transgene expression test for finished product batch release (recommendation). The major objection is considered solved.

Batch release acceptance criteria for the following parameters were requested to be tightened as the proposed limits were considered not to have been clinically qualified and not to reflect process capability for safety, concentration and potency assays. This was considered a Major Objection. In the response, the applicant has tightened the acceptance criteria for all requested assays. The proposal is acknowledged and acceptable. Acceptance criteria are expected to be reviewed once more manufacturing experience is available (recommendation).

Infectivity is of prime importance as only infectious viruses can elicit an immune response to the SARS-CoV-2 spike protein. The shelf life specification originally proposed for the number of infectious viruses was substantially lower (about 4-6 times) than are present in batches used in the clinical trials. The applicant was requested to clinically justify the shelf life limit for infectivity or increase the shelf life limit to a level that was considered clinically justified. If necessary, the release limit would also be tightened. This was raised as a Major Objection. In the submitted response, the applicant proposed changes in acceptance criteria.

However, an adequate clinical justification for an acceptable immunogenicity or efficacy at this dose level was still lacking. The applicant was requested to clinically justify the shelf life limit for infectivity or increase the shelf life limit to the lowest infectious virus dose that shows adequate immunogenicity or efficacy. If necessary, the applicant was requested to change the release and/or shelf life limit. Further tightening of the acceptance criteria was subsequently proposed.

From a clinical perspective, the end of shelf-life limit corresponds to the low dose (LD) which was given in clinical studies COV002 and COV005. It is known that this dose resulted in a reduced immune response compared to the standard dose and the clinical relevance of this lower response is not known. If boosted with a standard dose (SD), there is no clear reduction in the immune response for subjects who received a low dose as first dose (LDSD) as compared to subjects who received two standard doses (SDSD). In the pandemic, the low dose study information can support these limits but given that the proposed limits cannot be fully justified by the data from the clinical studies, the applicant is requested to investigate this further after approval (Specific obligation 2).

Some uncertainty around the shelf life specification may be acceptable in the context of a conditional marketing authorisation. Also, considering the public health crisis and urgent need, it will be unlikely that vaccines will be stored to their end of shelf life (expiration date).

The applicant is recommended to further review the FP release acceptance criteria once further manufacturing experience is available (recommendation).

Due to the implementation of ICH Q3D guideline on elemental impurities, compliance to ICH Q3D should be confirmed. Although vaccines are strictly taken, not within the scope of ICH Q3D, a risk assessment of the elemental impurity level in the FP should be performed in order to keep the same level of safety assurance on elemental impurities as in the past, as requested according to Ph. Eur. general chapter 5.20. The applicant

has committed to provide a summary of this risk assessment and a control strategy for elemental impurities in accordance with ICH Q3D by March 2021 (recommendation).

The risk of n-nitrosamine contamination was addressed in line with current guidance and no risk of n-nitrosamine contamination was identified.

The FP manufacturing process consists of AS thaw, pooling if required, dilution, mixing and fill-finish operations and therefore, no new impurities are introduced. Information on AS impurities can be found in the AS characterisation section.

Analytical methods

Analytical methods that are used for AS and FP have been submitted in the AS section. A brief summary for the FP specific analytical methods has been provided and reference to the specific pharmacopeia methods has been presented for compendial methods.

Batch analysis

Batch analysis data for all clinical processes have been provided. The results are consistent, some differences have been observed in the product strength as measured using different methods during clinical development although this does not have an impact on the dose administered (see comparability assessment for further details).

Commercial batches (Process 4) manufactured at Catalent Anagni, CP Pharmaceuticals and IDT Biologika have been submitted, however many analytical tests were pending for Catalent Anagni and CP Pharmaceuticals. As highlighted in the manufacturing process section, batches manufactured at IDT are consistent. Nevertheless, the applicant was requested to present the missing data or withdraw CP Pharmaceuticals and Catalent Anagni from the EU FP manufacturing sites as it had not been shown that these sites are able to manufacture FP according to the release specifications which are comparable to the clinical process. This was considered a Major Objection. In the submitted response, the applicant presented additional batch release data for the three sites. The data presented demonstrate process consistency, quality and comparability to clinical FP, sufficient to support approval of a conditional marketing authorisation for this product although pending data from each of the sites is requested post-approval to complete the validation data (Specific obligation 1).

Reference materials

The reference standard used for the FP is the same as for the AS. Please refer to the AS reference materials section.

Stability of the product

The proposed shelf life for AZD1222 finished product is 6 months at the intended storage condition of 2-8 °C.

A summary of all clinical and commercial FP batches placed in stability studies has been presented. The stability studies are mostly aligned with ICH Q5C guidelines. Studies are conducted at 2-8 ^{o}C and 23-27 ^{o}C.

The primary stability lots are three Process 3 clinical batches. The container closure used is representative of the commercial container closure system. Likewise, the stability indicating assays used in those studies are the same as used for the Process 4 AS stability studies. Stability data has been presented for at the long-term storage temperature 2-8 °C. All batches meet the stability acceptance criteria. Stability data are

available for all batches at accelerated conditions at 25 °C. A decrease in infectivity and viral particle/infectious particle ratio has been observed. In addition, supporting stability data are presented for clinical lots derived from Process 1 and Process 2. Overall, the three Process 3 clinical batches are considered representative of the commercial batches taking into consideration that comparability has been demonstrated and the available data support the 6 month shelf life claim at 2-8°C.

Additional commercial scale FP batches have been placed in stability studies.

The applicant has presented the stability protocol for process 4 commercial batches, which is adequate.

The applicant has committed to perform a photostability study. Results should be submitted post-approval (recommendation).

After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to the administration for no more than 48 hours in a refrigerator (2°C – 8°C). Within this time period the product may be kept temporarily at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. It cannot be returned to the refrigerator.

The primary stability data are considered sufficiently representative to support commercial FP storage for the purposes of this MA. However, the FP storage period must be confirmed with stability data for process 4 lots of all FP manufacturing sites and FP presentations applied for. Completed process 3 and process 4 stability studies should be provided post approval (Specific obligation 2). In addition, the applicant is requested to recalculate the rate of average loss of infectivity during FP storage at 2-8 °C when further stability data becomes available. If necessary, the release specification should be changed in order to ensure that batches will remain within shelf life specification during storage and handling (Specific obligation 2).

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

A finished product shelf-life of 6 months at 2-8ºC is accepted.

Adventitious agents

The applicant has identified the raw materials of human/animal origin used during the manufacture of AZD1222 vaccine and has provided the source, suppliers and certificates of origin. Certificates of Suitability for materials of bovine origin have been provided. A TSE/BSE risk assessment for these materials with high risk of TSE has been conducted, concluding that the risk of TSE transmission is extremely low.

Testing of cell banks/virus seeds for viral agents has been performed in accordance with guidelines ICH Q5A(R1), ICH Q5D and Ph. Eur. 2.6.16. All cell banks produced at CBF Oxford, Cobra or AZ have been adequately tested for the presence of adventitious viral agents. Although the absence of RCA is tested for during routine production, the applicant should provide the results of the RCA testing of the master virus seed (MVS) phenotypic stability at passage 5 when available (recommendation).

The MHCBs and WHCBs were tested for mycoplasma and sterility. MHCB and WHCB test results met the acceptance criteria. The MVSs and WVSs were tested for mycoplasma and either sterility or bioburden.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Control cell cultures for virus seeds were tested for bioburden. MVS, WVS and control cell culture test results met the acceptance criteria.

Bulk viral harvest (BVH) samples taken directly from the bioreactor prior to harvest and lysis as well as production host control cell samples taken directly from the control culture prior to harvest are tested for mycoplasma and bioburden. No contaminating microorganisms were detected is the specification. The AS and FP are tested for bioburden and sterility, respectively.

In summary, the adventitious agents safety evaluation performed on the different cell banks and virus seeds is considered acceptable.

Post approval change management protocol(s)

PACMP- Replacement or addition of a new manufacturer of the active substance
The applicant has submitted a PACMP for the addition of new AS manufacturers to ensure the continuity of AS supply for AZD1222. The protocol proposes to manage the authorisation of additional AS sites that will have been demonstrated to produce AS which is comparable to that produced in currently approved AS manufacturing sites.

The additional AS sites will operate in accordance with GMP; no significant changes to the approved AS manufacturing process, batch size or process control; container closure, shelf life and storage conditions will be introduced; equivalent materials will be used in the AS manufacturing process; no changes to AS/FP specifications; no changes proposed to AS release, stability testing procedures or control sites; analytical methods appropriately validated; no changes proposed to approved FP manufacturing process, parameters, CPPs, IPCs or container closure as a consequence of the AS change; the manufacturing process for the additional AS site will be validated in accordance with the proposed validation protocol and the quality of the AS material will be assessed in accordance with a comparability protocol.

PACMP conditions include the production of at least three representative AS batches manufactured at commercial scale and placed on long term stability for the new AS site, that will be qualified by a receiving FP manufacturing site by producing at least one batch of FP at commercial scale, manufactured in accordance with approved MA conditions. This FP batch will be placed on long-term and accelerated stability assays and results will be provided for the implementation of this PACMP.

However, qualification data for the new AS supplier will not be reported as part of the PACMP implementation.

A detailed comparability assessment will be conducted on AS and FP, including routine release and characterisation tests and stability assessment. The comparability testing plan is described. The testing plan for the FP manufactured using AS produced at the new site is also described.

Results from process validation, analytical method qualification and comparability assessment will form part of the FP quality assessment for the change and will be provided when reporting implementation of this PACMP.

In addition to the studies detailed below a AS transportation assessment will be performed for each proposed new AS manufacturer.

The applicant proposes to submit a Type IB procedure to implement the changes proposed for this PACMP.

The applicant should update the PACMP with the comments received from the CHMP and the agreed validation and comparability protocols (recommendation)

PACMP- Replacement or addition of a manufacturing site for Part or all of the manufacturing process of the finished FP

The applicant has submitted a PACMP for the addition of new FP manufacturing sites that will have been demonstrated to produce FP which is comparable to that produced in currently authorised FP manufacturing sites.

To support the use of the PACMP, the additional FP site will operate in accordance with GMP; no significant changes to the approved FP manufacturing process, batch size or process controls; container closure, shelf-life and storage conditions remain unchanged; equivalent materials used in the FP manufacturing process; no changes to FP release or stability specifications or procedures; no changes in the sites responsible for batch control or secondary packaging; transfer of analytical methods and manufacturing process for the additional FP site will be appropriately validated.

Quality of the FP material manufactured by the new site will be assessed in accordance with the comparability protocol provided in the PACMP.

At least three consecutive process validation batches (at commercial scale) will be manufactured at the proposed new FP site and placed on long-term stability. A process validation protocol is presented. A detailed comparability assessment will be conducted on the FP. In addition, three FP batches will be placed on long-term stability for stability trending comparability.

The applicant proposes to submit a Type IB procedure to implement the changes proposed for this PACMP.

The PACMP is considered adequate for the addition of a new FP manufacturer when there are no significant changes proposed to the FP manufacturing process as detailed in the eCTD Section 3.2.P.3.2 of the approved marketing authorisation

GMO

Refer to the ERA.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The quality information for the COVID-19 Vaccine AstraZeneca presented during the MAA has been thoroughly assessed. A list of questions was generated, which included 8 Major Objections, related to GMP, specifications, reference standard, comparability ranges, acceptance criterion for infectivity during shelf-life and limited or no data on validation and comparability of the material from three active substance and three finished product manufacturing sites to those used in clinical studies.

Adequate responses were provided for specifications, comparability ranges, acceptance criterion for infectivity and the reference standard to support Conditional Marketing Authorisation. Additional validation, release and comparability data have been submitted for AS and FP manufacturing sites. Necessary EU GMP certificates for the manufacturing and testing sites were subsequently provided.

Further information is provided below on the resolution of the major objections and the rationale for accepting some open issues to be addressed as specific obligations post-marketing. Several other issues are further highlighted as recommendations to be addressed by the applicant post-approval.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

The dossier is of acceptable quality, however, certain information and data remain to be provided. Despite the short time frame of product development, sufficient data to support conditional marketing authorisation are provided and key areas requiring completion are explained below. These further data will be addressed in specific obligations and other post-approval measures (recommendations).

Information on the manufacturing process and process controls for the manufacturing sites is provided. The manufacturing processes are similar between the three commercial manufacturing sites (Henogen, BE; Catalent, USA; Oxford Biomedica, UK) and batches are produced at the commercial scale; the main differences are related to equipment and facility fit. There are three sites for AS manufacture and data from other sites has also been used as supportive information. Overall, data from a number of GMP-grade lots manufactured using the commercial process and at commercial scale were submitted.

Currently available process validation data for all the process steps are provided. The applicant has provided validation data of batches manufactured at all facilities. Validation has however not been finalised. In the absence of complete validation data, available process performance data are provided from individual lots, including lots manufactured prior to process validation, using the same process and scale and manufactured in the same facilities as the validation lots.

In conclusion, sufficient data have been provided to support the conclusion that all sites are able to consistently manufacture active substance (AS) of good quality in the context of a conditional marketing authorisation in an emergency situation. However, final validation data from each site intended for commercial manufacture have not been provided and are required to complete the dossier to substantiate that conclusion (Specific obligation 1).

The comparability between clinical manufacturing processes and commercial Process 4 has been evaluated using batch release and characterisation results and degradation trends of AS manufactured by clinical Process 3 and commercial process 4 at accelerated stability conditions. The applicant's chosen comparability ranges were questioned during the procedure and additional justification was presented for their establishment. The justification presented by the applicant is considered acceptable, however, the acceptance ranges should be revised for future comparability exercises when more manufacturing experience is available (recommendation).

During initial assessment it could not be concluded that commercial Process 4 AS is comparable to Process 1, 2, 3 AS for all three AS sites until further results were evaluated. The applicant provided further comparability data for all three commercial sites. For this conditional marketing authorisation in an emergency situation, these data sufficiently demonstrate comparability of AS manufactured at these sites to

AS used to formulate product used in clinical studies. However, completion of the comparability data package is requested to confirm this conclusion (Specific Obligation 1).

The proposed specifications for active substance are acceptable with respect to the attributes chosen for routine release testing. However, the active substance specifications acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available in line with manufacturing process capability (recommendation).

An AS shelf life of 6 months at -90 to -55°C is agreed. Although the stability data were limited, the applicant has provided data from lots manufactured by Process 3 (clinical process) at a facility not intended for commercial manufacture. Results are available for long-term conditions up to 4 months, 3 months and 2 months. The container/closure system for these batches is one of the proposed commercial storage containers, Pall Allegro Bags. In the context of the conditional marketing authorisation and given the comparability of the commercial process to the clinical batches, this is deemed sufficient to support the proposed shelf life but the applicant should provide additional AS stability data and analysis to confirm the storage period using process performance qualification (PPQ) lots manufactured at each AS commercial site (Specific Obligation 2).

Finished product

The finished product is a multi-dose (8 or 10-dose) ready-to-use suspension for intramuscular injection of chimpanzee adenovirus vector encoding the SARS-CoV-2 spike protein.

The development of the manufacturing process is sufficiently described. The description of the manufacturing process and process controls for the three intended manufacturing sites in the EU are acceptable. The manufacturing processes are similar between the three manufacturing sites; the main differences are related to equipment and facility fit. The commercial scales are specified for Catalent Anagni, IT and CP Pharmaceuticals, UK and IDT Biologika, DE. Overall, data from a sufficient number of GMP-grade lots manufactured using the commercial process and at commercial scale were submitted.

Detailed PPQ validation protocols for the three manufacturing sites have been provided. In summary, a minimum of three consecutive process validation lots are being produced in the three manufacturing sites. The currently available set of validation data although not complete, are reassuring and support that the product can be manufactured consistently. All results of performance outputs are within acceptance criteria and also the process parameters remain within their acceptance criteria or range. The applicant submitted further validation data for the three sites during the procedure which sufficiently support that each site can consistently manufacture product of high quality. Pending data are nevertheless required post-approval to complete the data package and to confirm this conclusion (Specific obligation 1).

Further to information provided by the Official Medicines Control Laboratory (OMCL) during finalisation of the MAA procedure regarding results from their independent testing and preliminary investigation of one batch of finished product from the Catalent FP site which suggested that the batch might not be homogenous, further information was requested from the applicant regarding corrective actions and determination of root cause analysis. Further investigation by the applicant and OMCL is underway. The company's root cause analysis will be provided post-authorisation upon completion. Mitigation measures have been put in place to require the company to introduce enhanced sampling during filling at all sites and testing of these samples using an absorbance method, which is considered the most suitable test to monitor homogeneity (Specific obligation 1). With the measure to further investigate the preliminary data suggestive of lack of homogeneity in one lot, the mitigation measures to introduce enhanced sampling and the requirement to finalise the PPQ data, which

also investigates homogeneity, the manufacturing process is considered to be suitably controlled to support the conditional marketing authorisation in an emergency situation.

A comparability assessment has been performed to demonstrate that the intended commercial FP process 4 is comparable to the clinical processes. The analytical assessment comprises all commercial batch release tests and additional characterisation tests. The applicant's chosen comparability ranges were questioned during the procedure (see active substance section above) and ranges of clinically relevant quality attributes were tightened and additional justification was presented. During the procedure, further comparability data for product from all three commercial FP sites were provided. The data suitably demonstrate comparability to clinical FP to support approval of a conditional marketing authorisation in an emergency situation although pending data from each of the sites is required to complete the package and confirm this position (Specific obligation 1).

The finished product specifications include a comprehensive panel of relevant tests along with corresponding acceptance criteria. However, the FP specifications acceptance limits should be re-assessed, and revised as appropriate, as further stability data are available (recommendation).

With respect to the finished product release and stability specification for infectivity, the originally proposed limits were increased to ensure that FP infectivity remains above that of the unintended low dose used in some clinical studies. This is acceptable in the pandemic scenario. However, since the clinical relevance of this lower response is not fully known further investigation of this issue is required after approval. The applicant is also requested to further review the FP release acceptance criteria for this potency assay once further manufacturing experience is available (Specific obligation 2).

The agreed shelf life for the finished product is 6 months at 2-8°C. A summary of all clinical and commercial finished product batches placed in stability studies has been presented. The primary stability lots are three Process 3 clinical batches manufactured at a non-commercial site. Stability data has been presented for batches at the long-term storage temperature. All batches meet the stability acceptance criteria. In addition, supporting stability data are presented for clinical lots derived from Process 1 and Process 2. Overall, the three Process 3 clinical batches are considered representative of the commercial batches given that comparability has also been demonstrated. The primary stability data are considered sufficiently representative to support commercial FP storage for the purposes of this conditional marketing authorisation. However, the FP storage period must be confirmed with stability data for process 4 PPQ lots from all FP manufacturing sites and all requested FP configurations (vial presentations). Completed process 3 and process 4 stability studies should be provided post approval (Specific obligation 2).

Finally, given the rapid development of this product, there are a number of issues which have been raised as recommendations in order to complete the dossier.

Impact on the benefit-risk assessment

Efficacy, safety and immunogenicity was demonstrated using clinical batches of the vaccine.

The active substance and finished product are acceptable in relation to control of critical quality attributes and impurities.

Studies to demonstrate batch-to-batch consistency of the active substance and finished product in terms of process validation studies/process performance qualification studies (PPQ) have not been fully completed in the active substance and finished product commercial manufacturing sites. Nonetheless, sufficient data have been provided for full scale lots (including some PPQ lots) at the commercial sites and at other sites using the commercial process. Preliminary data suggestive of lack of homogeneity in one lot is being investigated and

mitigation measures to introduce enhanced sampling to ensure batches are consistent have been put in place. These data and measures put in place lead to the conclusion that the risk of inconsistency in product quality is low.

Similarly, due to the speed of development in the pandemic scenario a comprehensive package to demonstrate comparability of these PPQ lots to clinical material has not yet been provided. However, the comparability data provided for the full-scale lots (including some PPQ lots) manufactured at each site do support a conclusion that the commercial product will be comparable to clinical material. The validation and comparability data will be completed using a concurrent validation strategy based on approved validation and comparability protocols with approved acceptance criteria. As a specific obligation the applicant will provide the completed process validation and comparability data for all of the commercial manufacturing sites.

The proposed specifications, as demonstrated by the submitted data, are suitable to control product quality. However, the lower shelf life limits for the infectivity specification are not fully confirmed and this could have potential impact on product potency. Despite this, sufficient clinical data have been provided to support the lower infectivity specification limit for authorisation and with this specification, a negative impact on product potency is considered unlikely. Due to the speed of development, real-time stability data for active substance and finished product are limited but data from clinical material are considered representative to support the respective AS and FP shelf-life. As a specific obligation the applicant will provide additional AS and AS stability data and will review the infectivity release and shelf life specifications as additional clinical data becomes available.

It is considered likely that the applicant will be able to provide the requested data and thereby fulfil the specific obligations.

Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment in order to complete all proposed specific obligations. Based on the applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted progressively between Feb 2021 and June 2022.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The data presented to support consistent quality of this medicinal product is considered to be sufficient in the context of a conditional marketing authorisation in the current (COVID-19) pandemic emergency situation. To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the specific obligations (SOs) post-approval.

The CHMP has identified specific obligations to address the quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed in Annex III.

In accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods (see the proposed recommendations in Annex III).

To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs) post-approval.

SO1: In order to confirm the consistency of the active substance and finished product manufacturing process, the applicant should provide additional validation and comparability data and, introduce enhanced testing.

Active substance

a. The applicant should provide specific dates for data completion for each site as follows: for current pre-process performance qualification (PPQ) and PPQ active substance (AS) batches, additional test release and characterisation data as well as new results for the degradation stability studies should be completed for Catalent Maryland, MD, US; Oxford Biomedica, Oxford, UK and Henogen S.A., Seneffe, BE to confirm that the process is properly validated. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021.

b. The applicant should provide specific dates for data completion for each site as follows, including for PPQ batches to be manufactured: complete final PPQ validation reports and comparability analysis (for three AS batches) must be performed for Catalent Maryland, Inc.; Henogen S.A.; and Oxford Biomedica (UK) Ltd. active substance manufacturing sites. Complete batch release and analytical comparability data (including degradation trend comparison) for PPQ batches should be presented to confirm that the process is properly validated and to demonstrate that the commercial AS is representative of the material used in clinical trials. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021.

Finished product

c. The applicant should provide the final FP comparability data and analysis for CP Pharmaceuticals and Catalent Anagni to demonstrate that the commercial product is representative of the product used in clinical trials. Responses to be provided no later than February 2021.

d. The applicant should provide the pending results and final PPQ reports of the three FP process performance qualification lots (including CPP; IPC and NCPP) manufactured at IDT Biologika ,CP Pharmaceuticals and Catalent Anagni and update section P.3.5.2.1 to confirm that the process is properly validated. Responses to be provided no later than March 2021.

e. The applicant should provide the final results for the additional FP in process testing performed as part of the process validation specifically at Catalent Anagni and CP Pharmaceuticals, (AS post-shipping and thawing studies, mixing test studies, hold test studies and product homogeneity) to confirm that the process is properly validated. Section P.3.5.2.1. should be updated. Responses to be provided no later than March 2021.

f. The applicant should introduce an enhanced sampling strategy for the FP filing process at all sites, at the beginning, at 25%, 50%, 75% and 100% of the filling process no later than February 2021 in order to confirm batch to batch consistency. At least 2 vials per sample should be tested using a rapid test capable of providing sufficient assurance of batch homogeneity i.e. measured by an absorbance. For this test the applicant should set justified acceptance criteria for homogeneity and the batch results should meet these.

SO2: In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.

Active substance

a. The applicant should provide additional AS stability data and analysis to confirm the storage period. This includes data following storage at -90 to -55°C, 2-8°C and 23-27°C/55-65% RH storage conditions for (Process 3 and 4) Pre-PPQ lots and for 3 PPQ lots manufactured at each AS commercial site. Updates should be provided upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than May 2022 with interim, monthly updates beginning February 2021.

Finished product

b. The applicant should provide additional finished product (FP) stability data to confirm the storage period with process 4 lots from all FP manufacturing sites and all requested FP configurations (FP presentations). Process 4 PPQ stability study updates should be provided post approval upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than June 2022 with interim, monthly updates beginning March 2021.

c. The applicant should recalculate the rate of average loss of infectivity during FP storage at 2-8 °C when further stability data of three PPQ batches from each commercial site becomes available. If necessary, the release specification should be changed in order to ensure that batches will remain within shelf life specification during storage and handling. The applicant should report the recalculation periodically until sufficient data are available to fully justify the release specification. Responses to be provided no later than December 2021 with interim, 3-monthly updates beginning May 2021.

d. The applicant should provide additional clinical justification for the end of shelf life FP infectivity specification. Additional immunogenicity data from clinical studies for participants primed and boosted with a Low Dose (LDLD), as well as a characterisation of breakthrough cases, i.e. the infectivity characteristics of the batches with which these individuals were immunised, should be evaluated as soon as available. Responses to be provided no later than September 2021.

2.2.6. Recommendations for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CHMP recommends additional points for investigation as listed below.

Quality recommendations are covered in the list of recommendations in Annex I.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

Immunogenicity and efficacy of AZD1222 were studied in different animal models including mice, pigs, ferrets and NHPs.

In both ferret and NHP studies, animals were challenged with SARS-CoV-2 strains without the Spike protein variant D614G (study report 20-01125: SARS-CoV/Australia/VIC01/2020; study reports 6284 and 6285: SARS-CoV/Vero/hSLAM/Victoria/1/2020), while this variant has emerged as predominant clade in Europe (66%) and worldwide (44%) (Isabel et al., 2020; https://doi.org/10.1038/s41598-020-70827-z). The Applicant has provided data related to Mean Neutralising Titres (Calculated from Log2-Values) to three circulating Australian SARS-CoV-2 containing D614G mutation in the spike protein. Data was obtained from sera in ferrets after prime-boost vaccination with AZD1222, administered via intramuscular and intranasal route. Data is indicative of relevant neutralizing titers induction to the three isolates, with IM administration being the route with the highest mean of neutralizing titers reported in all three instances. The highest titers were detected in the D614 variant SA01 compared to the D614 variant VIC01 and the G614 variant VIC31.

Mice

A study was conducted in mice (Graham et al 2020) in which the immunogenicity of one or two doses of AZD1222 (10^8 infectious units) in an inbred (BALB/c) and outbred (CD1) mouse strain (and pigs, see below) was compared. Intracellular cytokine staining (ICS) of splenocytes showed, in both mouse strains, that the response was principally driven by $CD8^+$ T cells. The predominant cytokine response of both CD8+ and $CD4^+$ T cells was expression of IFN-γ and TNF-α, with negligible frequencies of IL-4^+ and IL-10^+ cells. There were no significant differences in $CD4^+$ and $CD8^+$ T cell cytokine responses between prime-only and prime-boost mice.

Another study carried out with two strains of mice (BALB/c, n = 5 and outbred CD-1, n = 8) for the immunogenicity assessment of the vaccine candidate (Van Doremalen et al, 2020) was provided. Animals received a single dose of AZD1222, 6 x 10^9 vp/animal IM or ChAdOx1 GFP (control). Assessment of the immunogenicity responses were measured 9- and 14-days post-dosing. IFN-γ ELISpot testing in blood mononuclear cells (PBMCs), stimulated with a peptide library spanning the full length of the spike (pools of S1 or S2 peptides) was employed. Total immunoglobulin IgG was identified against S1 and S2 proteins in all vaccinated mice. Titres against S1 where higher in CD-1 mice compared to BALB/c.

As expected, neutralizing antibodies were only reported in test article-dosed animals but not in controls, and at a higher extent in CD-1 mice compared to BALB/c mice. IFN-γ results are more comparable in both rodent strains, although levels were slightly higher for BALB/c. Increased $CD4^+$ and $CD8^+$ populations were observed in both strains after immunization. Increases were notably higher in the $CD4^+$ subtype compared to $CD8^+$ in CD1 mice.

Non-human primates

Efficacy and/immunogenicity in non-human primates (rhesus macaques) were assessed in two studies: Van Doremalen et al, 2020, and study 6284.

In the study described in Van Doremalen et al, 2020, animals received one (prime only) or two doses (prime-boost) of AZD1222 with 2.5×10^{10} vp/animal (half the dose used in clinical trials) 28 days before challenge in the prime boost only group. The prime-boost group received a second immunization 4 weeks after the first dose and was also followed by SARS-CoV-2 challenge 28 days later. Challenge occurred by intranasal, intratracheal, oral and ocular routes (total challenge dose of 2x106 TCID50 SARS-CoV-2). Animals were subsequently followed up to seven days.

Prime-only related data is indicative of IgG titre increase in ELISA at 11 and 28 days post-vaccination, nevertheless a decrease in neutralizing antibodies was seen 28 days post-dosing compared to 11 days post-dosing. Those results were similar in the prime-boost group, although showing a higher response compared to single dose. ELISpot responses were significantly higher in prime-only animals compared to prime-boost, while no significant response was seen in GFP prime-boost controls. The different subtypes of IgG measured were not provided.

Cytokine measurements following challenge revealed highly variable IFN-γ levels in prime-only animals on Day 1 post-challenge, but a much lesser upregulation in prime-boost animals at the same time point. All other cytokines measured (i.e., TNF-α, IL-2, IL-4, IL-5, IL-6, IL-10 and IL-13) did not show relevant changes post-challenge.

Clinical scores in prime-vaccinated animals were minimally reduced when compared to prime-boost vaccinated monkeys. Viral load in tissues at 7 DPI presents a difficult interpretation since prime-only data is not that different compared to data from prime-boost vaccinated animals.

Prime-boost vaccination before challenge did not result in improved clinical scores up to 7 days post-challenge compared to single dose vaccination, thus both vaccination regimens being comparable at this time point.

BAL gRNA and sgRNA levels reported were low and similar between prime-only and prime-boost vaccinated animals compared to high levels seen in controls. Nose swab total viral RNA did not show a clear difference among groups, while lung tissues from vaccinated animals appear to have less gRNA and sgRNA levels compared to controls, although data presented a high variability.

There was an unexpected finding of viral RNA in tissues of the gastrointestinal tract at 7 days post-challenge in immunized animals, but not in the control group. The Applicant states that "…there is a trend towards greater presence of viral RNA in the gastrointestinal tract in the 5 prime-boost group animals with a strong antibody response prior to the very high dose challenge." In addition, the clinical scores were worse in the prime-boost group compared to the prime-only group. The Applicant exerts that the significance of this finding is not yet known

None of the vaccinated monkeys developed respiratory disease, in contrast with controls (2/3 animals developed mild pulmonary pathology).

Additional results from study 6284 (non-human primate immunogenicity and protection in rhesus macaques) were also provided. Three animals/sex were vaccinated with half the human dose (prime-only). Animals were challenged 4 weeks later by intranasal and intratracheal routes (total challenge dose of $2.5x10^6$ PFU SARS-CoV-2). Immunogenicity testing post-vaccination (D14, D27) and post-challenge (D3, D7, D14) was assessed. All but 2 vaccinated animals were reported as healthy throughout the challenge follow-up and an additional animal was reported to display laboured breathing 12 days post-challenge.

Neutralizing antibodies were seen only in vaccinated animals but not in controls (PBS) and a very high variability was observed. It is currently unclear whether humoral response is associated with protection.

In this study on the day of challenge, no difference between vaccinated and control animals was observed in the T cell response, and the number of activated $CD8^+$ T cells in peripheral blood was even significantly lower in vaccinated animals compared to controls. The decrease in activated $CD8^+$ T cells on day 0 (day of challenge) could not be explained. Focusing on specific subsets showed that activation of $CD4^+$ and $CD8^+$ T cells (i.e., HA-DR^+) was observed 3 days post-challenge in the vaccinated group compared to the control group.

Leucocyte levels were reported to be stable from Day 0 to Day 7 post-challenge in vaccinated animals, while a decrease was seen in controls. Of note, neutrophils displayed a reduction in both vaccinated and control groups, but it was less evident in vaccinated monkeys. Also, the monocyte to lymphocyte ratio and the monocyte population were elevated in vaccinated animals after challenge compared to controls. High monocyte to lymphocyte ratio may suggest a worse clinical condition in COVID-19 patients (Sun S et al., Clin Chim Acta. 2020 Aug; 507: 174–180. doi: 10.1016/j.cca.2020.04.024). Activated cytotoxic T cells were increased following challenge in vaccinated animals and controls. Reduction of $CD4^+$ and $CD8^+$ T cell counts was also reported in both groups, but less evident in vaccinated monkeys. Subtyping of the cellular immune responses and long-term immunity/protection are generally limited in the dossier across studies. The Applicant confirmed that no subtyping was performed other than $CD4^+$ and $CD8^+$ T cells.

Computerized tomography (CT) scan score was assessed on Day 5 and Day 12 after challenge. Data reveal a lower CT score at Day 5 in vaccinated animals compared to controls, but no relevant differences and findings between both groups were seen by Day 12. The relevance to humans is unknown.

qPCR testing at baseline confirmed that in all animals, RNA testing was below the assay LOQ. BAL timepoint sampling revealed reduced viral RNA copies at 7, 13 and 14 post-challenge in vaccinated animals. Viral RNA was significantly lower on Day 7 post-challenge in BAL at necropsy in vaccinated animals compared to controls, nonetheless subsequent measurements revealed that no significant differences were seen at 13/14 days post-challenge for controls.

No clear distinction regarding adverse findings were reported in lung provided histopathology data between controls and vaccinated animals at 13/14 days post-challenge.

The final report of study 6284 included the data from the Plaque Reduction Neutralisation Titre (PRNT) assay and the age of the animals. Since some inconsistencies were observed in the submitted data, appropriate amendments including a summary and a discussion of these data should be incorporated to the updated dossier.

Ferrets

The Applicant studied the immunogenic response to the vaccine and the protection upon challenge in ferrets by means of two complementary studies: the first one aimed at measuring viral replication (20-01125), the second one was focused on the histopathological features and included the use of a potential Th2-biased immunisation using formalin-inactivated SARS-CoV-2 (6285). In study 6285, ferrets were challenged with $5x10^6$ PFU, equivalent to approximately 1.0 $x10^7$ $TCID_{50}$. In study 20-01125, ferrets were challenged with $3x10^4$ $TCID_{50}$ SARS-CoV-2. In both cases the challenge was applied 4 weeks after the last vaccine dose.

Ferrets only develop mild effects in response to SARS-CoV-2 infection (they do not develop lower respiratory tract disease as observed in humans). In both studies, comparisons between regimens involving prime-only and prime-boost were performed, with an interval of 4 weeks between prime and boost when required and employing a dose level of $2.5x10^{10}$ vp per administration per animal. The studies were conducted by using the IM route, as this is the intended clinical route of administration. For study 20-01125, two additional

groups of animals were vaccinated by the intranasal route, which was afterwards compared to the intramuscular route.

Both studies intended to address the immunogenic response to the vaccine. However, limited information has been provided regarding T cell responses, in the context of only one of the studies conducted in ferrets.

Although neutralizing antibodies were reported using different approaches, which make comparison between studies difficult, the same pattern can be identified in the antibody response. For both studies, prime-only vaccination induced a response in neutralizing antibodies that was subsequently increased upon exposure to the challenge. When prime-boost was addressed, a marked increase in NAbs was detected 7 days after the second exposure to the vaccine, reaching a peak and showing a marked decreased after another 7 days. The levels were then stable and no subsequent increase was detected upon exposure to the challenge. In more detail, for study 6285 with regard to neutralizing antibodies after challenge, for group 1 (AZD1222 prime only) no significant difference was detectable between sample days (D0, D2, D6 and D13-14); for group 2 (AZD1222 prime-boost) due to the variability in response between animals, no significant differences between timepoints were detected; in group 3a and 3b (GFP prime only and prime-boost), neutralizing antibody levels were below the assay limit of quantification in samples from the 2 vector control groups at the time of challenge and for the first week post-challenge. However, neutralizing antibodies were measured at a higher level in samples from animals culled at 2 weeks post-challenge and the magnitude of neutralizing antibody response in control animals does not appear to be different from that in vaccinated animals. Finally, in the last group of animals, group 4 (formalin inactivated SARS-CoV-2), all animals showed increases in neutralizing antibodies from 0-2 and 2-6DPC, whilst levels in most animals plateaued during the second week post-challenge. Pairwise comparisons all reached statistical significance except 6-15DPC.

The generation of NAbs following the IN route was lower in magnitude compared to the IM route in both prime-only and prime-boost regimens, but the responses in viral shedding seem to be better in the IN prime-boost compared to the prime-boost IM group.

Following challenge, no histological abnormalities developed in vaccinated and control animals in study 20-01125. In study 6285, mild pulmonary lesions were observed in control animals, with a reduced severity in animals vaccinated with AZD1222 and a temporary increased severity (i.e. exacerbation) in animals vaccinated with formalin-inactivated SARS-CoV-2 one week post-challenge. One week later, differences in lung pathology no longer existed between test groups, most likely because the pathological scores from the AZD1222 vaccinated animals increased and the scores for the formalin-inactivated SARS-Cov-2 vaccinated animals decreased. No significant differences were found between groups 1 (prime-boost) and 2 (prime only). This is the only immune-related measurement conducted in the study.

Viral replication in the lower respiratory track was absent in study 6285 and no differences in viral RNA quantification were evident in the upper respiratory tract when comparing prime-only and prime-boost animals.

There is more than a 300-fold difference in the challenge doses applied in both studies (study 6285 vs 20-01125). It should be noted that in the study which used the lower dose for the challenge (20-01125), none of the animals developed clinical signs or were minimal.

There was a reaction upon challenge observed in some animals in the first study (20-01125), that the Applicant ascribes to presence of BSA in the challenge virus stock. The probable root cause of this adverse event was identified as a medium component, foetal bovine serum (FBS). Ferret sera were shown to have significant levels of antibodies reacting to a component of the FBS (BSA).

Pigs

The study in pigs was conducted with the aim of study the immunogenic response to the vaccine in a large animal model (Graham et al 2020). The original publication compared responses in mice and pigs, but only the results from pigs are shown in this section.

Although carried out with a limited number of animals (3 animals per dose regimen), which limits the statistical analysis to be performed over the generated data, a trend towards increased response upon boost is identified in this study. Though a formal negative control is absent, the prime-only animals can be used as a surrogate control for the prime-boost group. Immune responses have only been followed for 6 weeks after the prime vaccination and reference to the individual animals per measure parameter have not been provided. This hampers the possibility to draw firm conclusions regarding a potential relationship between high neutralising antibody responses and (Th1-biased) T cell responses and on the value of a second immunisation and the duration of the immune response. Nevertheless, the study results show a trend towards higher humoral and cellular responses in animals vaccinated with the prime-boost regimen. The addition of a second dose of the vaccine in pigs is capable to induce a sustained Nabs response, at least for a short period of time measured in the study (14 days).

Secondary pharmacodynamic studies

No studies on the secondary pharmacodynamics have been performed, which is in accordance with applicable guidelines.

Safety pharmacology programme

A cardiovascular and respiratory safety in mice (study 617078) dosed with $2.59x10^{10}$ vp AZD1222 showed no effects on blood pressure, heart rate and respiratory parameters. In the repeat-dose toxicity study 513351 in mice, effects of AZD1222 on autonomic, neuromuscular, sensorimotor, behavioural parameters and effects on body temperature and pupil size were assessed in an Irwin Screen in conscious male mice in the morning on Day 8 and Day 29. Following intramuscular administration of AZD1222 at a viral particle dose of $3.7x10^{10}$, there were no effects on body temperature, pupil size or Irwin Screen observations.

Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been performed, which is in accordance with applicable guidelines.

2.3.2. Pharmacokinetics

AZD1222 is replication-incompetent in human cells due to a block in gene expression caused by the deletion of the E1 genes. Therefore, after the initial infection of the cells upon viral entry, it is expected no further infection and therefore no spread of the virus within the body.

A single dose intramuscular biodistribution study with AZD1222 in mice is ongoing (study 514559).

A study with the same platform vector ChAdOx-1 has been performed (study 0841MV38.001), in combination with MVA, but carrying in both vectors a different insert which in this case codifies for a hepatitis B virus

insert. In addition, two studies conducted by the Applicant with a similar viral vector (ChAd63) have been presented to sustain the biodistribution and persistence of the product under assessment. The comparison of ChAd63 with ChAdOx1 has been discussed on the basis of their inclusion in the same Ad species (group E) and the same entry receptor (CAR). Although being a different adenovirus, ChAd63 is closely related to ChAdOx1 and the 2 viruses are believed to have similar infectivity and tissue tropism.

In neither of the studies conducted with AdCh63, presence of viral vector particles was observed beyond the injection site. AdCh63 ME-TRAP was administered intradermally instead of intramuscularly. In addition, the study with ChAd63 MSP-1 showed no evidence of replication of the virus or presence of disseminated infection. In both studies, the methods used for the determinations are not clearly defined and/or validated.

In the biodistribution study of the ChAdOx1 vector containing a hepatitis B virus (HBV) insert ($2.4x10^{10}$ vp), the product was administered once to BALB/c mice by IM administration (study 0841MV38.001). Other groups received a second dose of ChAdOx1-HBV on Day 28, but these groups also received an injection with MVA-HBV at Day 28. Although the insert is different, it is accepted that the insert would not drive a differential biodistribution of the vector. Samples for the biodistribution assessment were obtained 1 day after the administration of the test item: whole blood, injection site (skeletal muscle), brain, heart, draining inguinal lymph node, kidney, liver, lung, gonads, and spleen. Assessment of CNS, peripheral nerves or bone marrow was not conducted. Shedding assessment in urine and faeces was performed as well. Although the highest levels of viral vector were observed in the injection site, low levels of distribution to some samples of all tissues were also observed. No evidence of shedding was found. It should be noted that only one time point (24 hours post dose) was assessed for the group receiving a single dose of ChAdOx1-HBV, with a limited number of animals in the experimental group. Samples analysed after the second injection (with both ChAdOx1-HBV and MVA-HBV, analysis at D29 and D56) indicated that elimination of the viral particles occurred. However, it is noted that no validation of the PCR that was used as detection method was available.

There is an ongoing biodistribution study with AZD1222 following a single intramuscular injection in mice (study 514559). This study includes tissue analysis on timepoints between D2 and D29 (4 in total) and will employ a validated quantitative PCR (Q-PCR) detection method. Furthermore, it includes biodistribution assessment of bone marrow from the left femur, brain, spinal cord and sciatic nerve, among a complete list of tissues.

In view of the type of product, absorption, metabolism and excretion studies are not deemed necessary. Similarly, the absence of pharmacokinetic drug interaction studies and other pharmacokinetic studies is considered acceptable.

2.3.3. Toxicology

Repeat dose toxicity

Several platform studies using the same (ChAdOx1) or a closely related platform (AdCh63), have been used to support the safety of AZD1222. These included a study with AdCh63 MSP-1 (1.11×10^{10} vp) and AdCh63 ME-TRAP (0.78×10^{10} vp), a study with ChAdOx1-MERS and ChAdOx1-Chik (both $1x10^{10}$ vp) and a study with ChAdOx1 NP+M1 ($1x10^{10}$ vp).

All 3 studies complied with GLP and were performed in mice. Two doses of the respective vectors were intramuscularly administered with a 14 day-interval, followed by a 13 days observation period. In all 3

studies, low toxicity was observed, with no other relevant effects than those related to a normal immune response.

A pivotal study toxicity 513351 was conducted with AZD1222 in mice. Mice are considered a relevant species for toxicity assessment as they develop an immune response to the vaccine antigen. Mice were administered control or test item ($3.7x10^{10}$ vp/dose) on Days 1, 22 and 43. The recovery period consisted of 28 days after the last dose. Although the full human dose cannot be administered to mice due to their small size, the administered dose allows the toxicity assessment of the viral vector. SARS-CoV2 vaccine AZD1222 is proposed to be administered twice to adults at $5x10^{10}$ vp (4-6 weeks apart).

The main findings likely related to treatment observed so far are a slightly higher body temperature in AZD1222 males 4 hours after each dose that was comparable to controls by 24 hours, as well as changes in haematology and plasma chemistry parameters.

A mild decrease in levels of monocytes was observed on D45 in males and females (0.43x in males and 0.39x in females), consistent with the expected pharmacology effects. Globulin levels were mildly higher (1.2x) and albumin levels were mildly lower (0.9x) in treated animals compared to controls on D45. After the recovery period, there were no treatment-related changes in haematology parameters.

The local effects observed in the toxicity study with AZD1222, as well as in the studies with the ChAdOx MERS and Chikungunya vaccines are considered non adverse and related to the inflammatory reaction to the vaccines. No dedicated local tolerance studies are required for AZD1222.

Genotoxicity and carcinogenicity

No genotoxicity and carcinogenicity studies were carried out, in line with relevant guidelines. Studies evaluating genotoxicity and carcinogenicity are normally not required for viral vaccines. Since no adjuvants or novel excipients are used in this product, absence of those studies is considered acceptable.

Reproduction Toxicity

A preliminary DART study has been performed in mice (study 490838). AZD1222 was administered twice to each dam, via the intramuscular route: 16 female mice were given the vaccine 13 days prior to pairing and again on Gestation Day (GD) 6 for assessment of the embryofetal development phase (EFD); another group of 16 female mice were given the vaccine on GD 6 and again on GD 15 for assessment of the littering phase (dose levels $2.59x10^{10}$ vp). Additional groups of 16 females were included in both the EFD and littering phases and acted as control groups, receiving A438 Buffer on the same days as the animals given the test item. No test item-related effects were observed on female reproduction, foetal or pup survival and no abnormal gross pathology findings in pups or in dams were detected in either phase. There were no test item-related foetal visceral or skeletal findings. The results indicate that there is sufficient transfer of anti-S glycoprotein antibody via placenta (at GD17.5) and lactation (at LD14) in mice immunised with AZD1222. The dose administered to the mice is half the human dose, which is acceptable considering the composition of the vaccine. Results from the preliminary DART study, as well as results from a study in pregnant sheep and goats with a previously developed simian adenovirus vectored vaccine, ChAdOx1 RVF, did not indicate the occurrence of adverse effects in reproductive toxicity. The main DART study in mice is ongoing (study 490843). The final study report should be provided (LEG).

Local Tolerance

No stand-alone local tolerance studies were submitted. This is acceptable and in line with relevant guidance on non-clinical vaccine development since local tolerance was evaluated in repeated dose toxicity studies.

2.3.4. Ecotoxicity/environmental risk assessment

AZD1222 is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the Spike (S) glycoprotein of severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2). The ChAdOx1 viral vector was derived from the parental organism chimpanzee adenovirus Y25 (ChAdY25) which itself was genetically modified to make it replication-deficient.

AZD1222 is intended for intramuscular (IM) administration at a dose of 5×10^{10} viral particles (i.e. 0.5 mL of 1×10^{11} viral particles [vp]/mL). The vaccination course consists of two separate doses of 0.5 ml each, with the second dose approximately 4-12 weeks after first dose.

All potential hazards for both unintended recipients and the environment have been identified. Given the nature of the GMO (a replication-defective adenovirus derived from a chimpanzee adenovirus), the manufacturing controls, the route of administration, etc. it is concluded that the overall risk for human health and the environment is negligible. Whole genome sequencing of the current GMP-produced MVS after 5 passages showed that the sequence of the virus is stable. The conclusions on the ERA were not affected.

No monitoring of shedding in vaccinated individuals is planned. Equally, no monitoring of unintended recipients is considered necessary. Only reporting under the pharmaceutical regulations is envisaged. This is considered acceptable.

The wording provided in the product information is appropriate.

Any unused vaccine or waste material should be disposed of in compliance with the local guidance for genetically modified organisms or biohazardous waste. Spills should be disinfected using agents with activity against adenovirus.

2.3.5. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics

The Applicant has provided data for the evaluation of the pharmacology of AZD1222 upon administration in animal models. Data provided shows that AZD1222 immunization in BALB/c, CD-1 mice, ferrets, pigs and nonhuman primate models was immunogenic at different extent in these species. Assessment included data of humoral, cellular and functional immune responses.

In both ferret and NHP studies, animals were challenged with SARS-CoV-2 strains without the Spike protein variant D614G. The Applicant has provided data related to Mean Neutralising Titres (Calculated from Log2-Values) to three circulating Australian SARS-CoV-2 containing D614G mutation in the spike protein. Data is indicative of relevant neutralizing titers induction to the three isolates, with IM administration being the route with the highest mean of neutralizing titers reported in all three instances.

Mice

Two immunogenicity studies were conducted in female BALB/c and CD-1 mice, for the assessment of humoral and cellular immune responses. The first study (Graham et al., 2020) animals received one or two doses of AZD1222. In the second study (Van Doremalen et al., 2020), animals received only a single intramuscular immunization with AZD1222. The vaccine was immunogenic in both murine strains.

NHP

Immunogenicity and protection against SARS-CoV-2 challenge in non-human primates (rhesus macaques) were assessed in two studies: Van Doremalen et al, 2020, and study 6284.

In the study described in Van Doremalen et al, 2020 animals received one (prime-only) or two doses (prime-boost) of AZD1222 with 2.5×10^{10} vp/animal (half the dose used in the clinical trials) 28 days before challenge. The prime-boost group received a second immunization 4 weeks after the first dose and was also followed by SARS-CoV-2 challenge 28 days later. Challenge occurred by intranasal, intratracheal, oral and ocular routes (total challenge dose of $2x10^6$ $TCID_{50}$ SARS-CoV-2). Animals were subsequently followed up to seven days.

Prime-only related data resulted in IgG increase, although neutralizing antibodies showed a decrease at 28 days post-dosing compared to the measurement performed at 11 days. Similar findings in neutralizing antibodies were reported in animals immunized twice although, with a higher response. The different subtypes of IgG were not measured separately (or individually).

Although cytokines levels (i.e., TNF-α, IL-2, IL-4, IL-5, IL-6, IL-10 and IL-13) did not show relevant changes post-challenge, high variability was seen after single dose immunization on Day 1 post-challenge.

Clinical scores in prime-vaccinated animals were only minimally reduced when compared to prime-boost vaccinated monkeys. In the same line, the BAL gRNA and sgRNA levels reported were low and similar between prime-only and prime-boost immunized animals and therefore the benefit of a second immunization could not be observed.

Viral RNA was identified in tissues of the gastrointestinal (GI) tract at 7 days post-challenge in immunized, but not control, animals. Animals receiving two doses of the vaccine revealed viral RNA in the GI, in contrast with single dose and controls (only one animal positive). This unexpected finding was attributed by the Applicant to a trend in animals immunized twice, to present viral RNA in this organ with a strong antibody response prior to the very high dose challenge. It is also relevant that clinical scores were worse in this group compared to single dose immunization. Since no sound justification was provided to clarify this issue and taking into account that it is unknown the relevance of this finding to humans, the Applicant has been recommended to further address this issue after CMA (recommendation).

None of the vaccinated monkeys developed respiratory disease, in contrast with controls (2/3 animals developed mild pulmonary pathology). It is unknown whether long-term protection can be adequately achieved due to the short duration of post-challenge assessment.

Additional study results regarding immunogenicity and protection from study 6284 were provided in a single dose immunization regimen followed by challenge with 5.0×10^6 $TCID_{50}$ SARS-CoV-2 by intranasal and intratracheal routes.

The variable results observed in neutralizing antibodies makes it difficult to reach a conclusion, although the vaccine shows to be immunogenic in this animal model, as shown by an increase in neutralizing antibodies.

T cell response had shown no relevant differences between immunized and control animals and although a decrease in activated $CD8^+$ T cells on Day 0 (day of challenge) could not be explained, specific subsets showed activation of $CD4^+$ and $CD8^+$ T cells (i.e., HA-DR^+) 3 days post-challenge in the vaccinated group compared to the control group. Reduction of $CD4^+$ and $CD8^+$ T cell counts was also seen in both groups, but less evident in vaccinated monkeys. The Applicant confirmed that no subtyping was performed other than $CD4^+$ and $CD8^+$ T cells. This issue is superseded by the information to be provided within the clinical data.

The pathology caused by SARS-CoV-2 infection was determined by computerized tomography (CT) scans on Day 5 and Day 12 post-challenge and by histopathology analyses, but the data provided were insufficient to confirm protection by the vaccine. Lung histopathology revealed no clear difference between vaccinated animals and controls and disagreement was found in the dossier between data related to scores from the CT scans. As a result of this discrepancy, and considering the limitations of the histopathology determinations, it is unknown if the pathology assessment in this study is sufficient to prove any protection by the vaccine against the pathology caused by the SARS-CoV2 infection. In addition, inconsistencies between the final report for PRNT assay and the available nonclinical summary are noted, since some of the scores from the CT scan on day 5 and day 12 are not in agreement with the original data. Amendments in the dossier related to the age of the animals and the PRNT assay after challenge should be properly done according to the data provided (recommendation).

Ferret

Two ferret studies investigated the immune response elicited by the vaccine and the protection after challenge. It is now known that ferrets develop only mild disease in response to SARS-CoV-2 infection, with a much more marked pathology in the upper compared to the lower respiratory tract. In both studies comparisons were made between prime-only and prime-boost regimens, with the doses separated for an interval of 4 weeks. The lose level was 2.5×10^{10} vp per administration per animal by the intramuscular route. In study 20-01125 an additional group of animals was vaccinated by the intranasal route, which is especially interesting for viruses affecting the respiratory tract. However, the induction of a specific local immune response in this group of animals was not further assessed even though the generation of NAbs was lower in magnitude compared to the IM route and there was a trend for increased reduction in viral load in animals vaccinated IN, although not statistically significant when compared to the IM group. Interestingly, study 6285 included a group of animals that was inoculated with formalin inactivated SARS-CoV-2 as a control, intended to address potential vaccine-related enhanced respiratory disease (ERD). Limited comparisons could be established between both studies as there was a difference of almost 300x in the challenge dose applied in the studies, making the results from study 20-01125 less relevant than those collected through study 6285, in which the challenge dose was similar to that applied to NHPs. As a consequence of the lower challenge dose used in study 20-01125, none of the animals developed clinical signs and histological abnormalities, or those were mild at the most.

Limited assessments were made regarding the humoral and cellular immune response. Data on antibody subtypes, Th1/2-biased response, T cell subtyping and determinations of neutralizing antibodies after vaccination and challenge was rather limited and, in some cases, completely absent. For the T cell responses, only interim data derived from study 20-01125 has been provided, and the definitive results are still awaited (recommendation).

Regarding the measurements on neutralizing antibodies, a clear pattern was identified arising from both studies. Prime-only regimen induced a rise in NAbs that was further increased upon exposure to challenge. For the prime-boost regimen it was noticed that the response was short-lived after boost, presenting as a small increased followed by a decrease after 7 days. This pattern might be explained as a result of the high

antigen dose applied in ferrets that could lead to antibody response against the vector or to the fact that the primary response was still ongoing when the animals received the boost. Neither hypotheses are substantiated with data. Following challenge, there was a trend towards increase in the titer of NAbs, with values similar between control and vaccinated animals.

Regarding the histopathology as seen in study 6285, mild pulmonary lesions were observed in control animals in comparison with AZD1222 vaccinated animals. One week after the challenge, this difference was no longer detectable due to the fact that the pathology scores in the vaccinated animals worsened over time. In contrast, formalin inactivated SARS-CoV-2 animals which presented the worst pathology scores among all the experimental groups during the first week, showed a tendency for improvement after the first 7 days post challenge. No differences were seen between prime-only and prime-boost regimens.

Viral replication was measured in both studies and improvements in viral load in the upper respiratory tract were associated with AZD1222 vaccination. No explanation regarding the absence of viral RNA in the lungs of the ferrets has been provided, however, it is noted that this model shows lower titers in the lungs compared to URT, independently of the histopathology (Muñoz-Fontela C, et al. Animal models for COVID-19. Nature. 2020 Oct;586(7830):509-515). Some of the animals in study 20-01125 presented a reaction leading to death that was ascribed to the presence of BSA derived from the culture media used for virus growth. This can be a result of the pre-existence of anti-BSA antibodies derived from the required husbandry vaccination. The full report of this deviation has been requested for reassurance (recommendation).

Pigs

A single study was conducted in a small (but usual) number of animals. Prime-only and prime-boost regimens were compared exclusively. A trend towards increased humoral and cellular response was determined but reduced statistical analysis could be run due to the limited number of animals. However, a sustained NAbs response was measured for 14 days in those animals receiving a second dose of the vaccine.

Conclusion on primary pharmacodynamics

Although there is still a number of issues related to significant uncertainties related to the immune response and protection data in animal models, the overall assessment is considered favourable and data that is needed to finalize the assessment is not considered sufficiently relevant to block a positive opinion. Clinical data overrides most of the uncertainties and those issues that are considered necessary to be addressed from a non-clinical authorisation have been requested post-authorisation.

Cardiovascular and respiratory safety were assessed in mice (study 617078) dosed with AZD1222, showing no concerns. The potential effects on the CNS were addressed as part of the toxicity study (513351) showing again no concerns. Secondary pharmacodynamic and pharmacodynamic drug interaction studies are deemed not necessary for this type of product.

Pharmacokinetics

ADZ1222 is based on a replication-incompetent chimpanzee adenovirus. The biodistribution and shedding of ChAdOx1 and related viral vectors (ChAd63) have been assessed by means of different studies conducted in mice. Although being a different adenovirus, ChAd63 is closely related to ChAdOx1 and the 2 viruses are believed to have similar infectivity and tissue tropism. No concerns were identified in the platform and related vector studies but the relevance of the collected results is limited due to several flaws in design/methods, which triggered the initiation of a study addressing the biodistribution of AZD1222, which is currently ongoing.

For the studies performed with ChAd63, the quantification methods have not been properly validated and one of the studies used a different route of administration from that proposed for AZD1222 (intradermal instead of intramuscular). For both studies the viral vector was not detected beyond the injection site.

For the biodistribution platform study it was accepted that the insert would not drive the distribution of the product, which is rather determined by the backbone vector (in this case ChAdOx1). Therefore, the results of a biodistribution study carried out with the ChAdOX-1 vector codifying a HBV insert were provided in support of the application. The study design included a group of animals receiving a single dose of the product, with measurements performed solely at a single time point. Another study arm investigated the addition of a second dose of ChAdOX-1 HVB plus a dose of MVA-HBV separated 28 days from the first dose. Blood and different organs were examined, but assessment of CNS, peripheral nerves or bone marrow was not conducted. Upon administration of the product, the highest levels of viral vector were observed in the injection site, but the product was also present at low amounts in other tissues. For those animals that received two doses of the vector (the ChAdOx1-HBV and MVA-HBV treated group) the results indicated elimination of the viral particles over time (D29 and D56).

The ongoing biodistribution study with AZD1222 upon a single IM injection in mice (study number 514559) will supersede both platform and related vectors studies. The improved design of the study includes various time points, including early points and will employ a validated detection method. Additional tissues of particular interest for this application will be assessed, including bone marrow, brain, spinal cord and sciatic nerve, among a complete list of tissues as well as faeces samples. As this study is considered highly relevant and pivotal, the final study report has been requested post-authorisation. Should the results of these studies affect the conclusions on shedding risks, a revised ERA should also be presented (LEG).

Toxicology

For the toxicology assessment of the AZD1222 vaccine, the Applicant has submitted data obtained from several GLP compliant studies carried out in mice using different vaccines with the same (ChAdOx1) or a closely related platform (AdCh63). Assessment of these studies revealed low toxicity, with no other relevant effects than those related to the pharmacological immune-related effects of the vector administration. The studies are considered as supportive.

In addition, a pivotal repeated dose toxicity study with AZD1222 in mice was carried out. The data do not reveal causes of concern regarding safety.

A preliminary developmental and reproductive toxicology study in mice with intramuscular administration of AZD1222 was submitted and no relevant safety signals were identified. Transfer of the medicinal product in animal milk is currently unknown. The definitive developmental and reproductive toxicology study in mice is currently ongoing (study 490843). The results of this study are necessary for the final assessment of reproductive toxicology and consequently the final report should be provided by the Applicant post-authorisation as a LEG.

Other toxicity supportive studies carried out with the same platform in goats and sheep do not suggest relevant effects in reproductive toxicity.

Adenovirus infections are prevalent in all geographic regions worldwide. Nevertheless, wild-type adenoviral infection in pregnant women is generally not associated with congenital anomalies. No safety concerns are expected as a result of the administration to pregnant women of AZD1222 (which is a replication-incompetent adenovirus).

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Studies that assess the potential risk of germ-line transmission with AZD1222 have not been carried out. However, there is a substantial amount of scientific evidence concluding that adenoviral vector administration does not result in germ-line transmission. To date there are no reported cases of germ-line transmission of replication-deficient adenovirus in animal models or humans. Therefore, the risk of vertical transmission of AZD1222 is considered negligible and AZD1222 administration to humans is not expected to result in related adverse effects.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed concerns raised for the purpose of granting a conditional MA in emergency situation from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

The CHMP considers the following measures necessary to address the non clinical issues:

1. The ongoing biodistribution study with AZD1222 following a single intramuscular injection in mouse (514559) started Nov 2020 will supersede the ongoing study 0851MV38.001 using ChAdOx1 vector carrying the HBV insert (platform study). The protocol of the study 514559 was assessed and considered pivotal and highly relevant and as such the final report should be provided by the Applicant by 30 April 2021.
2. A DART study in mice with intramuscular administration of AZD1222 is ongoing. The final report should be provided by the Applicant by 30 April 2021.

Nonclinical recommendations and legally binding measures are covered in the list of recommendations in Annex I.

2.4. Clinical aspects

2.4.1. Introduction

This application is supported by four clinical studies: study COV001 (UK, Phase I/II); study COV002 (UK, Phase II/III); study COV003 (Brazil, Phase II/III) and study COV005 (South Africa, Phase I/II). An overview of these trials is provided in Table 4. For more details see section 2.5.

Evidence of immunogenicity and safety for AZD1222 based on data from all 4 studies based on a 4th of November data cut off. The pooled efficacy analysis was based on 2 studies, COV002 and COV003. The efficacy analysis was event-driven, and the cut-off date for the pooled analysis was the 7th of December 2020. Follow-up of participants is expected to continue until study end.

GCP

The applicant claimed that the clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, EMA, in the context of the COVID-19 pandemic, gathered additional information on clinical trial conduct and GCP compliance of the studies included in this dossier, from the UK Medicines and Healthcare products Regulatory Agency (UK-MHRA), and in collaboration with WHO from the South African Health Products Regulatory Authority (SAHPRA) and shared the outcome of the GCP inspections performed by those authorities with the CHMP, in order for this information to be considered in the assessment:

- UK-MHRA GCP inspection report for study COV001 "A phase 1/2 study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine in UK healthy adult volunteers"
- UK-MHRA GCP inspection report for study COV002 "A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19".
- SAHPRA GCP inspection report for study COV005 "An adaptive phase 1/2a randomized placebo-controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV".

Having considered all the above information, no GCP inspection of the clinical trials included in this dossier was requested by the CHMP.

- Tabular overview of clinical studies

Table 4: Overview of the studies included in the application

Element	COV001	COV002	COV003	COV005
Identifier	NCT04324606; EudraCT 2020-001072-15	NCT04400838; EudraCT 2020-001228-32	ISRCTN89951424	NCT04444674
Title	A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers	A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19	A Randomized, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine.	An adaptive phase I/II randomized placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 Vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV.
Region	United Kingdom	United Kingdom	Brazil	South Africa
Phase	I/II	II/III	III	I/II
Period	23Apr2020-ongoing	29 May2020-ongoing	Jun2020-ongoing	Jun2020-ongoing
Design	FIH, participant blind, randomised, controlled	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Double blind, randomised, placebo-controlled, adaptive
Primary study objective	To assess efficacy of AZD1222 against COVID-19; To assess the safety of AZD1222	To assess efficacy of AZD1222 against COVID-19 in adults aged ≥18 years Co-Primary: To assess the safety of AZD1222 in adults and children.	To evaluate the efficacy of AZD1222 against COVID-19 disease virologically-confirmed	For group 1 and groups 2a and 2b: To assess safety, tolerability and reactogenicity profile of AZD1222; Co-primary objective for groups 2a and 2b: To assess efficacy of AZD1222
Study population	Healthy adults aged 18-55 years	Main efficacy study: Healthy adults aged ≥18 years Priority given to health professionals and adults with high potential for exposure to SARS-CoV-2 Safety and immunogenicity substudies: Healthy children aged 5 to 12 years, inclusive HIV+ adults aged 18 - 55 years	Health professionals and adults with high potential for exposure to SARS-CoV-2, aged ≥18 years	Adults aged 18-65 years, living with and without HIV

Actual treatment	AZD1222: 2.5×10^{10} vp ; 5×10^{10} vp 0.5 mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) MenACWY: 0.5 mL	AZD1222: 2.2×10^{10} vp (qPCR) ; 2.5×10^{10} vp (qPCR) ; 5×10^{10} vp (Abs 260) ; 5×10^{10} vp (qPCR) 0.5 mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) MenACWY: 0.5 mL	AZD1222: 5×10^{10} vp 0. 5mL (3.5 - 6.5 × 10^{10} vp) MenACWY: 0.5 mL 0.9% saline solution: 0.5mL	AZD1222: 5×10^{10} vp; Normal saline (0.9% NaCl)
Primary efficacy endpoints	Virologically-confirmed symptomatic cases of COVID-19	Virologically-confirmed symptomatic cases of COVID-19	COVID-19 virologically-confirmed symptomatic cases	Virologically-confirmed COVID-19 cases occurring in participants that were COVID-19 naïve at the time of randomization and who received at least two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose.
Secondary efficacy endpoints (continued)	a) Hospital admissions associated with COVID-19 b) Intensive care unit admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Severe COVID-19 disease (defined according to clinical severity scales). e) Seroconversion against non-Spike SARS- CoV-2 antigens	a) Hospital admissions associated with COVID-19 b) Intensive care unit admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Seroconversion against non-Spike SARS-CoV-2 antigens e) Severe COVID-19 disease (defined according to clinical severity scales)	a) Hospitalization for COVID-19 virologically-confirmed; b) Severe COVID-19 virologically-confirmed; c) Death associated with COVID-19; d) Antibodies against SARS-CoV-2 non-Spike protein (efficacy against non-Spike seroconversion rates)	Endpoints in for the overall population and stratified by COVID-19 serological status at randomisation include: a) VE in preventing virologically-confirmed COVID-19; Per-protocol population analysis. Time frame: include all cases occurring onward from 21 days after a single dose or 7 days after a second dose (if a 2-dose schedule was adopted) b) VE in preventing virologically-confirmed COVID-19 cases VE in preventing virologically-confirmed moderate-severe COVID-19 c) VE in preventing hospitalization due to virologically-confirmed COVID-19 VE in preventing death associated with virologically- confirmed COVID-19 d) VE in preventing] all-cause LRTI (overall and stratified by hospitalization or not, irrespective of test result for SARS-COV-2)
Planned total enrolment	1090	12390	10000	2070
Control	MenACWY	MenACWY	MenACWY	Saline

Number of doses	One or two (based on study group)	One or two (based on study group)	Two	Two
AZD1222 dose levels	Standard and Low	Standard and Low	Standard and standard	Standard and Low
Prophylactic treatment	Paracetamol for a portion of participants	Paracetamol for a portion of participants	Paracetamol systematically	As clinically needed

2.4.2. Pharmacokinetics

No pharmacokinetics studies have been conducted for AZD1222. This is because pharmacokinetics studies are generally not needed for vaccines, consistently with current Guidelines on clinical evaluation of vaccines.

2.4.3. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, in line with the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

Mechanism of action

COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The ChAdOx1 (AdvY25) viral vector is replication-deficient as the E1 gene essential for replication has been deleted. Thus, the virus can only propagate in cells expressing E1 functions but is unable to replicate within vaccinated animals or humans. Following administration, the S glycoprotein is expressed locally and stimulates a humoral and cellular immune response.

Currently there is no established correlate of protection for COVID-19.

Primary and Secondary pharmacology

The bioanalytical methods used to assess serostatus at baseline as well as immunogenicity induced by the vaccine include measurement of:

- Humoral immunogenicity, which was analysed by means of: i) a validated multiplexed immunoassay which quantitatively measured binding antibodies to SARS-CoV-2 antigen N, S and RBD in human serum, ii) a validated pseudoneutralisation assay using a lentiviral vector platform at an IC_{50}, and iii) a qualified live neutralisation assay using a virus strain derived from SARS-CoV-2 Victoria/1/2020 analysed at the Neutralisation Dilution 50 measurement (PRNT50).
- Cell-mediated immunity, which was assessed by two different methods: i) IFNγ ELISpot to examine the ability of PBMCs stimulated with overlapping Spike (S) peptide pools to produce IFNγ, and ii) an ICS assay to characterise and phenotype the response of PBMCs to overlapped S peptide pools.

Validation or qualification reports have been submitted for the main assays, including the SARS CoV-2 neutralising antibody assays. Although additional clarifications are requested to be provided post-authorisation, the overall conclusion is that the assays used can be considered fit for purpose. For the pseudoneutralization antibody assay, clarification was requested around specificity and cross-reactivity of the assay, as well as specific questions on the biological matrixes and limits of detection. Questions on the live neutralizing antibody assay centred around the number of clinical specimens that fell above and below the ULOQ and LLOQ, respectively. Additionally, data on the master virus used in the qualification and the robustness of the assay were posed to the applicant. Further details on the size of the validation data set for the qualitative assay to assess nucleocapsid antibodies by electrochemiluminescent were posed as well as

clarification on the mechanism for qualifying the peptides used in the IFNγ ELISPot assay. This information will be provided post-approval.

Anti-vector Immunity

Considering the low prevalence in humans of Chimpanzee adenoviruses, the choice of the ChAdOx1 chimpanzee adenoviruses would minimize the impact of pre-existing immunity in humans to adenovirus.

The Phase 1/2 COV001 study designed to evaluate safety and immunogenicity of AZD1222, demonstrated that anti-vector (i.e. anti ChAdOx1) responses are induced after a single dose of AZD1222. These anti-vector responses do not increase following a second dose (Folegatti et al 2020b, Barrett et al 2020).

No specific immunogenicity trial has been performed to compare the SARS-CoV-2 immune response induced in subjects seropositive and seronegative to ChAdOx1 at the time of immunization. The immune response in some subjects in study COV002 that previously received a vaccine based on ChAdOx1 vector was examined. S-binding ELISA results show that after the second AZD1222 dose S-binding titres were similar (705 EU versus 692.5 EU, respectively) in participants presumed to be ChAdOx1 seronegative and those previously treated with a ChAdOx1 vector, respectively. Therefore, the impact of pre-existing anti-vector immunity is expected to be minimal in the context of a 2-dose vaccine regimen.

Dose and Regimen Selection

The choice of the dose for AZD1222 was based upon previous experience with ChOx1Ad-MERS vaccine. A Phase 1 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). 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. Additionally, T cell responses to the Spike immunogen of MERS-CoV were seen in all dose levels. This conclusion is supported by platform data with ChAdOx1 vectors containing alternative immunogens at the dose of 5×10^{10} vp (Dicks et al 2012; Dudareva et al 2009; Folegatti et al 2019).

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 increasing neutralising antibody titres. Neutralising antibody responses against SARS-CoV-2 were detected in 91% of participants after a single dose when measured by MNA80 and in 100% of participants when measured by PRNT50. These data were confirmed in larger numbers of study participants (52 subjects) after a second dose of either standard or low dose strength (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, which is in agreement with previously published reports describing the induction of Th1-type human IgG subclasses following adenoviral vaccination.

The initial intent of this programme was to implement a one-dose only immunization schedule. Following review of immunogenicity data from COV001, which showed that a second dose increased immunogenicity, a decision was made to start testing a 2-dose schedule. As a result, and due to logistical issues, there is a variation on dosing intervals across the clinical studies presented, mainly affecting the UK studies COV001 and COV002. The interval between doses 1 and 2, originally intended to range from 4 to 12 weeks, ranged from 4 to 26 weeks.

Immunogenicity results

Immunogenicity was evaluated in the context of the four pivotal studies (COV001, COV002, COV003, and COV005) based on a data cut of November 4th. The details on the methodology and the designs of these trials are included in the clinical efficacy section. The proposed vaccination course for studies COV001, COV002, COV003, and COV005 consisted of two separate IM doses of 5×10^{10} vp AZD1222 each. Due to a potency miscalculation of some batches, some subjects in trial COV002 received a first dose with half the amount (called low dose -LD- approximately 2.2×10^{10} vp) of the intended dose (called standard dose – SD- 5×10^{10} vp, corresponding to not less than 2.5×10^{8} infectious units).

The population for analysis covering immunogenicity are described as follows:

Population	Description
LD/SD for Immunogenicity	Only participants in Any Dose for Safety who received LD/SD of AZD1222 or in corresponding control group. Participants without at least one post-baseline immunogenicity result will be excluded. The treatment assignment will follow the same rule of Any dose for safety analysis set. This analysis set will be used for immunogenicity analysis.
SD/SD + LD/SD for Immunogenicity	Only participants in Any dose for Safety who received LD/SD or SD/SD of AZD1222 or in corresponding control group. Participants without at least one post baseline immunogenicity result will be excluded. The treatment assignment will follow the same rule of Any dose for safety analysis set. This population will be used for the immunogenicity analysis.
SD/SD for Immunogenicity	Only participants in Any Dose for Safety who received two SDs of AZD1222 or in corresponding control group. Participants without at least one post baseline immunogenicity result will be excluded. The treatment assignment will follow the same rule of Any dose for safety analysis set. This analysis set will be used for immunogenicity analysis.

Assessment of humoral and cellular immunogenicity were considered secondary endpoints. The immunogenicity endpoints were:

- SARS-CoV-2 Spike (S) and RBD antibody quantification (D0, 28 days after first dose, 28 days after second dose, GMTs and GMFRs)
- Virus NAb assays against SARS-CoV-2 (D0, 28 days after first dose, 28 days after second dose, GMTs and GMFRs)
- Antibody seroconversion rate (≥4-fold increase between D0 and D28) against SARS-CoV-2 S-protein, RBD and NAb
- Proportion with neutralizing titres (> LLOQ), Nab (data pertaining to this endpoint were not provided).

Seroresponse is defined as a ≥4-fold rise in titres from the day of dosing baseline value to 28 days post each dose.

Humoral Immunogenicity

Approximately 15% of the overall safety analysis set was included in the immunogenicity analysis set, with more samples analysed on the Spike/RBD binding assays as compared to the cell-based pseudoneutralisation assay due to logistic constraints. The selection of subjects for the immunogenicity analysis set was based on a pragmatic approach. This was not a random selection which likely is the reason for the imbalances between the treatment groups in terms of demographics and baseline characteristics. As these imbalances are small, no substantial impact on treatment differences is expected. The immunogenicity analysis set was enriched for participants ≥65 years of age, and more AZD1222 participants as compared to control participants were included.

Table 5: Disposition of Participants in Pooled Analysis Sets

Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	Control	Total
All participants randomized					12018	11735	23753
Immunogenicity							
SD/SD + LD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SD/SD LD/SD	All available timepoints	1666	1205	2871
SD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SD/SD	All available timepoints	1367	1031	2398
LD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	LD/SD	All available timepoints	299	174	473

a Analyses on these sets use data starting from first dose.
b Analyses on these sets use data starting from ≥ 15 days post the second dose.
c Analyses on these sets use data starting from ≥ 22 days post the first dose.
LD = low dose; Neg = negative; Pos = positive; SD = standard dose.
Source: Main Safety Tables 1.1.1.1 and 1.1.1.2; Immuno Table 1.1.1.2

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. All data discussed in this section pertain to seronegative participants at baseline, unless otherwise stated.

The rate of seroconversion (≥4-fold increase from baseline) by S-binding antibodies was ≥98% at 28 days after the first dose and > 99% at 28 days after the second dose for seronegative participants at baseline in the pooled combined (SD/SD + LD/SD) immunogenicity analysis set, as well as in both the SD/SD and LD/SD analysis sets. 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.

Geometric mean titres for S-binding antibodies and neutralizing antibodies are shown in the next Table for both seropositive and seronegative participants at baseline for each of the three analysis sets (combined SD/SD + LD/SD, SD/SD and LD/SD).

Table 6: Quantification of SARS-CoV-2 antibody levels by serostatus (Immunogenicity Analysis Set)

SARS-CoV-2 S-binding Antibody Levels						
			SD/SD+LD/SD		**SD/SD**	**LD/SD**
Subgroup	**Timepoint**	**Statistic**	AZD1222	Control	AZD1222	AZD1222
SEROSTATUS		N	1655	1197	1356	299
Seronegative	Baseline	n / N_{sub}	950 / 1617	769 / 1166	882 / 1320	68 / 297
		GMT	**57.18**	**55.47**	**57.18**	**57.21**
		(95% CI)	(52.9, 61.8)	(51.0, 60.3)	(52.8, 62.0)	(44.0, 74.3)
	Post Dose 1	n/N_{sub}	885/1617	704/1166	817/1320	68/297
		GMT	**8156.07**	**56.85**	**8386.46**	**5836.18**
		(95% CI)	(7563.3, 8795.3)	(51.6, 62.6)	(7758.6, 9065.1)	(4340.4, 7847.4)
	Post Dose 2	n/N_{sub}	886/1617	705/1166	819/1320	67/297
		GMT	**30206.20**	**62.70**	**29034.74**	**48986.76**
		(95% CI)	(28271.0, 32273.9)	(56.3, 69.8)	(27118.2, 31086.7)	(38483.3, 62357.0)
Seropositive	Baseline	n / N_{sub}	30 / 38	28 / 31	29 / 36	1 / 2
		GMT	**13137.17**	**10966.21**	**13137.97**	**13114.00**
		(95% CI)	(7592.6, 22730.6)	(5260.4, 22861.0)	(7441.8, 23194.1)	(NE, NE)
	Post Dose 1	n/N_{sub}	29/38	28/31	28/36	1/2
		GMT	**178522.42**	**7303.99**	**175120.84**	**305936.00**
		(95% CI)	(123872.3, 257283.1)	(3307.9, 16127.4)	(120096.9, 255354.8)	(38483.3, 62357.0)
	Post Dose 2	n/N_{sub}	29/38	25/31	28/36	1/2
		GMT	**114488.67**	**8296.39**	**112978.13**	**166062.00**
		(95% CI)	(74664.2, 175554.8)	(4233.6, 16258.1)	(72553.8, 175925.4)	(NE, NE)
		N	1655	1197	1356	299
SARS-CoV-2 nAbs by Pseudoneutralisation						
Seronegative	Baseline	n / N_{sub}	798 / 1617	596 / 1166	629 / 1320	169 / 297
		GMT	**20.07**	**20.31**	**20.09**	**20.00**
		(95% CI)	(19.93, 20.21)	(20.00, 20.61)	(19.91, 20.27)	(NE, NE)
	Post Dose 1	n/N_{sub}	720/1617	599/1166	575/1320	145/297
		GMT	**55.47**	**20.47**	**55.56**	**55.12**
		(95% CI)	(50.61, 60.80)	(20.04, 20.91)	(50.21, 61.47)	(44.35, 68.51)
	Post Dose 2	n/N_{sub}	703/1617	555/1166	549/1320	154/297
		GMT	**175.07**	**21.45**	**166.24**	**210.53**
		(95% CI)	(160.59, 190.84)	(20.68, 22.24)	(150.42, 183.72)	(178.31, 248,57)
Seropositive	Baseline	n / N_{sub}	12 / 38	8 / 31	11 / 36	1 / 2
		GMT	**205.56**	**54.70**	**203.43**	**230.55**
		(95% CI)	(93.59, 451.49)	(16.37, 182.72)	(85.04, 486.62)	(NE, NE)
	Post Dose 1	n/N_{sub}	13/38	7/31	12/36	1/2
		GMT	**1663.06**	**51.75**	**1651.65**	**1806.29**
		(95% CI)	(1084.40, 2550.53)	(15.94, 168.05)	(1032.98, 2640.87)	(NE,NE)
	Post Dose 2	n/N_{sub}	13/38	5/31	12/36	1/2
		GMT	**887.21**	**71.50**	**919.41**	**578.34**
		(95% CI)	(594.92, 1323.10)	(14.48, 353.02)	(597.78, 1414.11)	(NE, NE)

Of note, baseline seropositive participants also had increased S-binding responses after a first dose, with a GMFR = 12.8 (95% CI: 7.0, 23.5) over baseline values. In contrast to the baseline seronegative group, antibody levels were not further increased by a second dose.

Humoral Immune Response by Subcategories

Adults with Comorbid Conditions at Baseline

No differences in immunogenicity were observed in the subcategory of participants with comorbidity compared with those without comorbidity, when examining binding antibody and nAb GMTs after both the first dose and second dose. Responses analysed in a live neutralisation assay confirmed this finding.

Country

The levels of S binding antibody induced after each dose in UK, Brazil, and South Africa in the three analysis sets (combined SD/SD + LD/SD, SD/SD and LD/SD) are shown in the next Table.

Table 7: Quantification of SARS-CoV-2 Antibody Levels by Country (Immunogenicity Analysis Set)

SARS-CoV-2 S-binding Antibody Levels						
			SD/SD+LD/SD		**SD/SD**	**LD/SD**
Subgroup	**Timepoint**	**Statistic**	AZD1222	Control	AZD1222	AZD1222
COUNTRY		N	1617	1166	1320	297
UK	Baseline	n / N_{sub}	584 / 1114	414 / 681	519 / 820	65 / 294
		GMT	**48.06**	**42.40**	**46.99**	**57.52**
		(95% CI)	(43.8, 52.8)	(38.2, 47.0)	(42.5, 51.9)	(43.9, 75.3)
	Post Dose 1	n/N_{sub}	575/1114	404/681	510/820	66/294
		GMT	**7322.20**	**43.12**	**7548.08**	**5769.13**
		(95% CI)	(6675.7, 8031.3)	(38.6, 48.2)	(6853.0, 8313.7)	(4237.7, 7854.0)
	Post Dose 2	n/N_{sub}	542/1114	367/681	478/820	64/294
		GMT	**34156.88**	**47.50**	**32384.99**	**50846.74**
		(95% CI)	(31333.9, 37234.2)	(41.7, 54.1)	(29560.8, 35479.0)	(39660.8, 65187.6)
Brazil	Baseline	n / N_{sub}	257 / 394	250 / 380	257 / 394	-
		GMT	**70.19**	**81.05**	**70.19**	-
		(95% CI)	(61.3, 80.3)	(69.9, 93.9)	(61.3, 80.3)	-
	Post Dose 1	n/N_{sub}	208/394	199/380	208/394	-
		GMT	**10013.29**	**81.09**	**10013.29**	**-**
		(95% CI)	(8504.8, 11789.3)	(68.4, 96.2)	(8504.8, 11789.3)	-
	Post Dose 2	n/N_{sub}	238/394	235/380	238/394	-
		GMT	**22305.42**	**79.72**	**22305.42**	**-**
		(95% CI)	(19905.8, 24994.3)	(4233.6, 16258.1)	(19905.8, 24994.3)	-
South Africa	Baseline	n / N_{sub}	109 / 109	105 / 105	106 / 106	3 / 3
		GMT	**89.48**	**64.83**	**90.92**	**50.92**
		(95% CI)	(67.0, 119.5)	(50.5, 83.2)	(67.6, 122.2)	(3.9, 669.2)
	Post Dose 1	n/N_{sub}	102/109	101/105	99/106	3/3
		GMT	**9859.17**	**85.25**	**9941.36**	**7496.44**
		(95% CI)	(8026.4, 12110.5)	(60.7, 119.7)	(8050.6, 12276.2)	(1461.4, 38454.7)
	Post Dose 2	n/N_{sub}	106/109	103/105	103/106	3/3
		GMT	**31828.30**	**97.45**	**32167.36**	**22121.36**
		(95% CI)	(26174.5, 38703.3)	(66.1, 143.6)	(26317.7, 39317.2)	(8547.7, 57250.2)
SARS-CoV-2 nAbs by Pseudoneutralisation						
	Baseline	n / N_{sub}	553 / 1114	384 / 681	385 / 820	168 / 294

		GMT	**20.00**	**20.00**	**20.00**	**20.00**
		(95% CI)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
UK	Post Dose 1	n/N_{sub}	495/1114	375/681	351/820	144/294
		GMT	**52.79**	**20.22**	**51.97**	**54.85**
		(95% CI)	(47.31, 58.90)	(19.91, 20.55)	(45.80, 58.97)	(44.07, 68.26)
	Post Dose 2	n/N_{sub}	494/1114	342/681	341/820	153/294
		GMT	**189.76**	**21.54**	**181.39**	**209.82**
		(95% CI)	(171.89, 209.48)	(20.50, 22.64)	(160.51, 205.00)	(177.54, 247.97)
Brazil	Baseline	n / N_{sub}	224 / 394	191 / 380	224 / 394	-
		GMT	**20.25**	**20.56**	**20.25**	**-**
		(95% CI)	(19.76, 20.76)	(19.79, 21.36)	(19.76, 20.76)	-
	Post Dose 1	n/N_{sub}	212/394	203/380	212/394	-
		GMT	**59.86**	**20.76**	**59.86**	**-**
		(95% CI)	(50.50, 70.96)	(19.71, 21.87)	(50.50, 70.96)	-
	Post Dose 2	n/N_{sub}	192/394	193/380	192/394	-
		GMT	**134.56**	**21.17**	**134.56**	**-**
		(95% CI)	(112.56, 160.87)	(20.12, 22.26)	(112.56, 160.87)	-
South Africa	Baseline	n / N_{sub}	21 / 109	21 / 105	20 / 106	1 / 3
		GMT	**20.00**	**23.97**	**20.00**	**20.00**
		(95% CI)	(NE, NE)	(18.47, 31.12)	(NE, NE)	(NE, NE)
	Post Dose 1	n/N_{sub}	13/109	21/105	12/106	1/3
		GMT	**105.54**	**22.08**	**104.93**	**113.22**
		(95% CI)	(41.45, 268.73)	(17.97, 27.13)	(37.60, 292.80)	(NE,NE)
	Post Dose 2	n/N_{sub}	17/109	20/105	16/106	1/3
		GMT	**328.67**	**22.53**	**327.23**	**352.54**
		(95% CI)	(208.63, 517.77)	(17.56, 28.92)	(201.20, 532.20)	(NE, NE)

For country, only the SD/SD results are taken into consideration, as Brazil did not contribute to the LD/SD group. Interestingly, while Brazil and South Africa have comparable S-binding antibody levels (GMTs) after the first dose (10,013 with 95% CI (8,504, 11,789) and 9,941with 95% CI (8,050, 12,276), respectively), there is a marked difference after the second dose (22,305 with 95% CI (19,905, 24,994) and 32,167 with 95% CI (26,317, 39,317)), although this is based on a small sample size and differences in the population demographics (e.g. age) or dose interval may account for this difference. Of note, both Brazil and South Africa seem to have slightly higher baseline GMTs as compared to UK participants. When the final clinical study results are provided, including the immunogenicity results, the applicant is requested to elaborate on whether this could be due to differences between laboratories. Further, an explanation of the difference in the proportion of participants in the 3 countries that contributed to the immunogenicity dataset, ranging from 100% (109/109) in the South African study, to 52.4% (584/1,114) in the UK study (all based on the seronegative SD/SD+LD/SD population), should be included (see section 4).

Older Adults (≥ 65 years of age)

The titres for S-binding antibodies and neutralizing antibodies (by Pseudoneutralisation) for subjects aged 18 to 64 and ≥65 years old are shown in the next Table.

Published data of immune response in healthy older adults suggested that immunogenicity by binding antibody and nAb responses were not numerically different from younger adults (Ramasamy et al 2020). The current report differs in that validated assays have been utilised and the sample size is larger and draws from a broader population that includes 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 below, section "Effect of dose interval on immune response").

Table 8: Quantification of SARS-CoV-2 Antibody Levels by Age (Immunogenicity Analysis Set)

SARS-CoV-2 S-binding Antibody Levels						
			SD/SD+LD/SD		**SD/SD**	**LD/SD**
Subgroup	**Timepoint**	**Statistic**	AZD1222	Control	AZD1222	AZD1222
AGE		N	1617	1166	1320	269
Age 18-64	Baseline	n /N_{sub}	805 / 1373	626 / 994	737 / 1104	68 / 269
		GMT	**59.38**	**59.47**	**59.58**	**57.21**
		(95% CI)	(54.6, 64.5)	(54.2, 65.3)	(54.6, 65.0)	(44.0, 74.3)
	Post Dose 1	n/N_{sub}	745/1373	567/994	677/1104	68/269
		GMT	**8610.76**	**61.87**	**8953.81**	**5836.18**
		(95% CI)	(7927.3, 9353.2)	(55.4, 69.0)	(8218.3, 9755.1)	(4340.4, 7847.4)
	Post Dose 2	n/N_{sub}	770/1373	598/994	703/1104	67/269
		GMT	**31969.52**	**68.07**	**30695.30**	**48985.76**
		(95% CI)	(29763.6, 34338.9)	(60.3, 76.8)	(28496.2, 33064.1)	(38483.3, 62357.0)
Age ≥65	Baseline	n /N_{sub}	145 / 244	143 / 172	145 / 216	-
		GMT	**46.40**	**40.87**	**46.40**	-
		(95% CI)	(37.9, 56.9)	(34.1, 48.9)	(37.9, 56.9)	-
	Post Dose 1	n/N_{sub}	140/244	137/172	140/216	-
		GMT	**6110.88**	**40.04**	**6110.88**	**-**
		(95% CI)	(5111.6, 7305.6)	(33.2, 48.3)	(5111.6, 7305.6)	-
	Post Dose 2	n/N_{sub}	116/244	107/172	116/216	-
		GMT	**20727.02**	**39.59**	**20727.02**	**-**
		(95% CI)	(17646.6, 24345.2)	(32.4, 48.4)	(17646.6, 24345.2)	-
SARS-CoV-2 nAbs by Pseudoneutralisation						
Age 18-64	Baseline	n /N_{sub}	720 / 1373	515 / 994	551 / 1104	169 / 269
		GMT	**20.08**	**20.36**	**20.10**	**20.00**
		(95% CI)	(19.92, 20.23)	(20.00, 20.71)	(19.90, 20.31)	(NE, NE)
	Post Dose 1	n/N_{sub}	645/1373	522/994	500/1104	145/269
		GMT	**58.12**	**20.37**	**59.03**	**55.12**
		(95% CI)	(52.69, 64.12)	(19.99, 20.76)	(52.87, 65.90)	(44.35, 68.51)
	Post Dose 2	n/N_{sub}	651/1373	501/994	497/1104	154/269
		GMT	**181.79**	**21.49**	**173.71**	**210.53**
		(95% CI)	(166.36, 198.66)	(20.67, 22.33)	(156.52, 192.78)	(178.31, 248.57)
Age ≥65	Baseline	n /N_{sub}	78 / 244	81 / 172	78 / 216	-
		GMT	**20.00**	**20.00**	**20.00**	-
		(95% CI)	(NE, NE)	(NE, NE)	(NE, NE)	-
	Post Dose 1	n/N_{sub}	75/244	77/172	75/216	-
		GMT	**37.10**	**21.11**	**37.10**	**-**
		(95% CI)	(29.26, 47.05)	(18.96, 23.49)	(29.26, 47.05)	-
	Post Dose 2	n/N_{sub}	192/394	193/380	192/394	-
		GMT	**109.21**	**21.07**	**109.21**	**-**
		(95% CI)	(77.58, 153.73)	(18.98, 23.38)	(77.58, 153.73)	-

Analysis by age category reveals, as expected, differences in GMTs based on age, with the higher response in the youngest age category.

The seroconversion rates (≥4-fold increase from baseline) 28 days post-second doses measured by the nAb (pseudoneutralisation assay) were similarly higher in younger adults than in elderly (80.7%, 95%CI 76.9-84.1 vs 64.0%, 95%CI 49.2-77.1).

Table 9: Summary of antibody seroconversion rate (≥4-fold rise compared to baseline) in SARS-CoV-2 Nab (Pseudoneutralization) by serostatus at baseline (SD/SD for immunogenicity analysis set) – Age at screening: 18-64 Years

	Seronegative		Seropositive		Total	
Parameter Visit Window	AZD1222 (N = 1104)	Control (N = 825)	AZD1222 (N = 31)	Control (N = 27)	AZD1222 (N = 1135)	Control (N = 852)
Day 28 post the first dose	482	376	10	4	492	380
>= 4-fold rise from baseline (seroresponse, %)	181 (37.6)	3 (0.8)	6 (60.0)	0 (0.0)	187 (38.0)	3 (0.8)
95% CI	(33.2, 42.0)	(0.2, 2.3)	(26.2, 87.8)	(NE, 60.2)	(33.7, 42.5)	(0.2, 2.3)
Day 28 post the second dose	482	365	10	4	492	369
>= 4-fold rise from baseline (seroresponse, %)	389 (80.7)	9 (2.5)	5 (50.0)	0 (0.0)	394 (80.1)	9 (2.4)
95% CI	(76.9, 84.1)	(1.1, 4.6)	(18.7, 81.3)	(NE, 60.2)	(76.3, 83.5)	(1.1, 4.6)

NAb = Neutralizing Antibody, GMT = Geometric Mean Titer, GMFR = Geometric Mean Ratio, CI = Confidence Interval, LLoQ = Lower Limit of Quantification, ULoQ = Upper Limit of Quantification, NE=Not Evaluable.
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.
Seroresponse is defined as >= 4-fold rise in titer level from the baseline level (i.e., the last non-missing measurement taken before Day 0 dose).
95% (or 97.5% one-sided for proportions of 0% or 100%) confidence intervals (CIs) for seroresponse rate are using Clopper-Pearson methodology.
Counts and summary statistics are based on participants who have non-missing titer values at baseline and the applicable visit.

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Table 10: Summary of antibody seroconversion rate (≥4-fold rise compared to baseline) in SARS-CoV-2 Nab (Pseudoneutralization) by serostatus at baseline (SD/SD for immunogenicity analysis set) – Age at screening: ≥65 Years

	Seronegative		Seropositive		Total	
Parameter Visit Window	AZD1222 (N = 216)	Control (N = 168)	AZD1222 (N = 5)	Control (N = 3)	AZD1222 (N = 221)	Control (N = 171)
Day 28 post the first dose	73	74	1	2	74	76
>= 4-fold rise from baseline (seroresponse, %)	14 (19.2)	1 (1.4)	1 (100.0)	0 (0.0)	15 (20.3)	1 (1.3)
95% CI	(10.9, 30.1)	(0.0, 7.3)	(2.5, NE)	(NE, 84.2)	(11.8, 31.2)	(0.0, 7.1)
Day 28 post the second dose	50	51	1	1	51	52
>= 4-fold rise from baseline (seroresponse, %)	32 (64.0)	1 (2.0)	1 (100.0)	0 (0.0)	33 (64.7)	1 (1.9)
95% CI	(49.2, 77.1)	(0.0, 10.4)	(2.5, NE)	(NE, 97.5)	(50.1, 77.6)	(0.0, 10.3)

NAb = Neutralizing Antibody, GMT = Geometric Mean Titer, GMFR = Geometric Mean Ratio, CI = Confidence Interval, LLoQ = Lower Limit of Quantification, ULoQ = Upper Limit of Quantification, NE=Not Evaluable.
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.
Seroresponse is defined as >= 4-fold rise in titer level from the baseline level (i.e., the last non-missing measurement taken before Day 0 dose).
95% (or 97.5% one-sided for proportions of 0% or 100%) confidence intervals (CIs) for seroresponse rate are using Clopper-Pearson methodology.
Counts and summary statistics are based on participants who have non-missing titer values at baseline and the applicable visit.

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Effect of dose interval on immune response

Spike-binding and neutralizing antibody titres after the first and second doses were analysed by dose interval for participants receiving either SD/SD or LD/SD (Table 11 and Table 12). The number of participants with available results in the LD/SD subset is generally low, with particularly few results from participants with shorter dose intervals contributing.

Table 11: Quantification of SARS-CoV-2 Spike antibody levels for different regimens (dose level and interval) (seronegative at baseline)

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

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

Table 12: Quantification of nAbs (by Pseudoneutralisation assay) levels for different regimens (dose level and interval) (seronegative at baseline)

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

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

There seems to be a relation between the dose interval and GMT (both Spike-binding antibodies as well as neutralising antibodies), which was observed both in the SD/SD as well as in the LD/SD group. Given that the far majority of the LD/SD group received the second vaccination ≥9 weeks after the first dose, in contrast to the SD/SD group who received the second dose mostly earlier, the observed differences in vaccine efficacy (see section 2.5) between the LD/SD and SD/SD groups seem to be more likely due to differences in dose interval rather than dose level. Of note, there is no indication of a difference between the LD/SD and SD/SD group when analysed by interval (e.g. 28 days after the second dose: LD/SD recipients with a ≥12 week interval (GMT 212 with 95% CI (169, 266), n=82) vs. SD/SD recipients with a ≥12 week interval (GMT 268 with 95% CI (221, 324), n=141). GMT titres were not measured at the time the second dose was administered, so it is not known how long titres persist after dose 1.

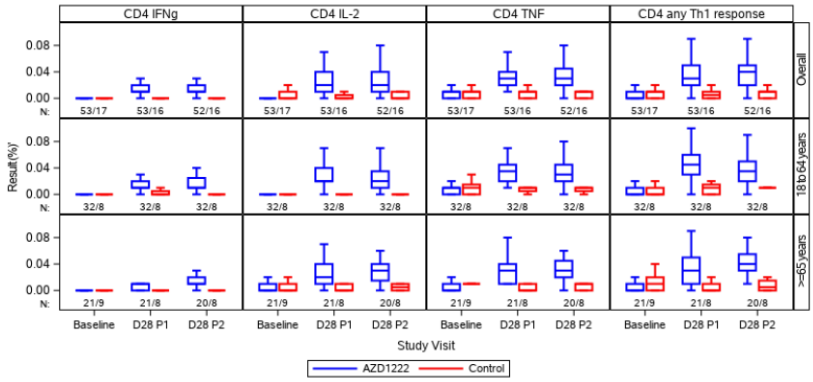
Cell-mediated Immunity

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 the ICS Analysis Set) was utilised to characterise the CD8 T cells with direct effector function (responsible for destroying virus-infected cells, preventing further spread of the virus after infection) and phenotype the response of PBMCs to overlapping Spike peptide pools. PBMCs were isolated from study participants in the UK COV001 and COV002 studies.

S-specific T cell responses as analysed by IFNγ+ ELISpot suggest that T cells are induced after a first dose of AZD1222 (with geometric means responses of 584 SFC/10^6 PBMCs) in the SD/SD + LD/SD baseline seronegative analysis set. No further increase was observed after a second dose (GMR = 421 SFC/10^6 PBMCs). IFNγ+ T cell responses were comparable between relevant subgroups (i.e., GMR = 681 SFC/10^6 PBMCs for subjects 18 to 64 years, 518 SFC/10^6 PBMCs for subjects ≥65 years; 630 SFC/10^6 PBMCs in subjects with comorbidities and 550 SFC/10^6 PBMCs in subjects without comorbidities), and did not increase after a second dose.

ICS was performed on 70 participants (40 aged 18 to 64 years; 30 aged ≥ 65 years) from the COV001 and COV002 studies, who received the SD/SD regimen. To assess the lineage, phenotype, and functionality of S-specific T cell responses, PBMCs were stimulated with S1 or S2 peptide pools containing overlapping 15- mer peptides from the full length Spike protein, fixed and stained for markers of Th1 response (IFNγ, IL-12, TNFα) or Th2 response (IL-4 and IL-13). Additionally, lineage (CD3, CD4, CD8) and activation markers were analysed (CD69, CD28, CCR7, CD45RA). At 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 2). These responses were generally similar between age categories, showing the same functional cytokine profile. Baseline levels of Th2 cytokine responses were minimal in both control and AZD1222 groups, with no increases 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 2: Th1 Cytokine Expression in SARS-CoV-2 S1 stimulated PBMCs



CD4 IFNg= CD+ IFNγ+; CD4 IL-2= CD4+ IL-2+, CD4 TNF= CD4+ TNFα+; CD4 any Th1 response= CD4+ with any of IFNγ+, IL-2+, TNFα+; D28 P1 = Day 28 post first dose; D28 P2 = Day 28 post second dose.
Source: Supplemental Figure IEMT60.1.1.1.
Additional figure for Th1 cytokine expression in SARS-CoV-2 S2 stimulated PBMCs presented in Supplemental Figure IEMT60.1.1.2.

Use of paracetamol

The prophylactic use of paracetamol was recommended before vaccination in all trials (except in COV005, and introduced as an amendment during COV001), and participants were advised to continue with 1 gram of paracetamol every 6 hours for 24 hours to reduce vaccine-associated reactions. Only a subset of participants was to report in their diary if they had taken paracetamol prophylactically or not. Prophylactic paracetamol use was not captured in the participant diary of study COV005.

There were exploratory objectives to describe safety, reactogenicity, immunogenicity and efficacy amongst those receiving paracetamol for 24h post-vaccination. The effect of paracetamol on immunogenicity was analysed by a standardised ELISA on participants in the COV001 study (Folegatti et al 2020). No differences in the generation of anti-S responses were observed in study participants who received paracetamol as compared to participants who did not.

2.4.4. Discussion on clinical pharmacology

Validation or qualification reports have been submitted for the main immunogenicity assays, including the SARS CoV-2 neutralising antibody assays. Although additional clarifications are requested that need to be provided post-authorisation (see section 4), the overall conclusion is that the assays that have been used can be considered fit for purpose.

There was no specific dedicated study to address the optimal dose concentration, the number of doses to be administered and the time interval between doses. The dose of 5×10^{10} vp, which was chosen for the larger studies with AZD122, was selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts. Following review of immunogenicity data from study COV001, a decision was made to use a two-dose schedule because the second dose increased the neutralising antibody titres and the percentage of subjects seroconverting. The recommended time interval between doses was set to be between 4- to 12-week. Due to 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 the second dose vaccinations in all 4 studies, though mainly affecting the UK studies COV001 and COV002. This resulted in the actual interval between dose 1 and 2 to range from 3 to 23 weeks. With hindsight, some dedicated dose finding trials may have been helpful in identifying the optimal dose and dose regimen before starting the pivotal efficacy trials. Both the relatively late decision to include a second dose in the pivotal efficacy trials as well as the accidental low dose given as a first dose – with its potential implication for efficacy – have complicated the interpretation of the clinical trials.

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. In total the number of subjects tested was 1666 subjects in the "SD/SD+LD/SD" set, which correspond to 1367 subjects in the SD/SD and 299 subjects in the LD/SD.

The seroconversion rates and the GMTs at baseline, and after first and second dose have been provided. Since the RBD-binding antibody response was closely correlated with the S-binding antibody response for all analyses, only the S-binding antibody response was presented. This approach is agreed. The rate of seroconversion (≥ 4-fold increase from baseline) measured by S-binding antibodies was ≥98% at 28 days after the first dose and >99% at 28 days after the second dose for seronegative participants at baseline in the pooled analysis set. Similarly, 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.

Differences were observed in SCRs between the 2 neutralisations assays, which are not fully explained. Overall, the live neutralisation assay may provide a more sensitive measurement of nAb titres than the pseudoneutralising antibody assay, which could be due to more particles per infectious unit in the pseudovirus assay than in the live nAb assay. More information is being requested post-authorisation (section 4).

In seronegative subjects at baseline there is an increase in antibodies after the first dose with a further increase after the second dose, a result that supported the 2-dose scheme. When comparing the SD/SD and LD/SD groups separately, the GMTs measured in terms of S-binding antibodies for the LD/SD group were numerically higher after the second dose compared with the GMTs for the SD/SD group (29,035 for SD/SD vs 48,986 for LD/SD, Table 6). This was also observed in the pseudoneutralisation assay GMT titres (Table 6). A higher immune response in the LD/SD dose group versus the SD/SD group is not fully understood. However, higher levels of neutralising antibodies were observed when the two doses were given at longer intervals, and the neutralising Ab response following SD/SD and LD/SD appeared consistent when stratified by dose interval. The fact that the time interval between the two doses affects the immune response adds another confounding factor to the interpretation of the vaccine efficacy results, since the SD/SD an LD/SD sets show important differences in the median time between the first and second dose (see section 2.5). It is noted however that the GMT titres were not measured at the time the second dose was administered (they were only measured 28 days after dose 1 and 28 days after dose 2); not knowing this further complicates interpreting the GMT titres reached after the second vaccination, e.g. it is not possible to understand to what extent the increase in GMTs seen after dose 2 is due to the interval at which dose 2 was administered, as seen with other vaccines.

The immune response was also assessed in the different subgroups (by serostatus, comorbidity, country and age). In participants who were seropositive at baseline, the immune response did not increase much after the second dose (GMT S-binding abs in LDSD+SDSD dataset: baseline 13,137.17 [95% CI 7592.6, 22730.6]; post-dose 1 178,522.42 [95% CI 123872.3, 257283.1]; post-dose 2 114,488.67 [95% CI 74664.2, 175554.8], which is consistent with an immune plateau noted with other vaccines. No differences were observed in GMTs in presence or absence of comorbidities. In relation to the immunogenicity results by country, differences were observed in the GMTs reached after the second dose, which were lower in participants from Brazil compared to UK and South Africa. As discussed in later sections, the efficacy in the UK and Brazil populations was similar, and in that way, it was unexpected to observe a lower immunogenicity in the participants from Brazil. It remains unclear whether this difference may be due to different baseline characteristics (such as age of participants, race) or to time interval between doses.

Regarding immunogenicity by age, GMTs were numerically lower in adults ≥65 years of age as compared to younger adults after both the first dose and second dose. This was observed for S-binding antibodies and neutralizing antibodies, (i.e., in the SD/SD seronegative population, the S-binding GMTs 28 days post dose 2 were 30,695 for adults 18-64 YoA vs. 20,727 in adults ≥65 YoA; pseudoneutralization GMTs 28 days post dose 2 were 174 in subjects 18-64 YoA vs. 109 in subjects ≥65 YoA). Also, based on the pseudo-neutralisation assay, seroconversion rates (SCR) were reduced in the elderly as compared to younger adults (the SCR was 81% in subjects aged 18-64 years and 64% in subjects ≥65 years of age). However it remains unknown if the relatively short dose interval in elderly may have impacted on the lower immune response, since the majority of participants ≥65 years old had a dose interval of <6 weeks. Since there is no established immunological surrogate that correlates with protection, the extent by which a lower immunogenicity translates into lower protection is unknown. However since elderly subjects mounted an immune response that is not dissimilar to the response seen in adults, a benefit from vaccination is expected

also in elderly albeit of unknown magnitude as reflected in the SmPC. Moreover, in order to obtain confirmation on the vaccine efficacy in this subgroup, the Applicant should submit the interim and final clinical study reports for study D8110C00001, which is an ongoing phase 3 confirmatory trial in approximately 30,000 subjects conducted in US, Chile and Peru, which includes a substantial number of older adults. The results of this trial are expected to confirm a vaccine efficacy estimate in important subgroups including in older adults and in subjects with underlying disease (see section 4).

S-specific T cell responses suggest that T cells are induced after a first dose of AZD1222 in the SD/SD+LD/SD analysis set. They do not increase after a second dose, consistent with published literature on homologous prime boost.

Based on ICS characterization of the immune response it is concluded that AZD1222 induces a S specific Th1 polarised response, which is reassuring in terms of lack of potential risk for VAED.

The immunogenicity results are obtained from interim results. Final study reports from pivotal studies COV001, COV002, COV003 and COV005 are requested to be submitted.

No immunogenicity data are available on the following aspects related to immunogenicity, which require further investigation post-approval: i) the need of a booster dose; ii) immunological correlate of protection, and iii) the ability of the vaccine to neutralize the emerging SARS-CoV-2 variants.

Regarding the latter, it is currently unclear whether AZD1222 immunization is able to induce a relevant response against recent SARS-CoV-2 circulating variants in Europe, since the induction of neutralizing antibodies to SARS-CoV-2 new variants was investigated only partially. Due to the relevance of this issue, the Applicant is requested to provide neutralising data on cross-neutralisation for clinically relevant and emerging SARS-CoV-2 strains by testing sera from human clinical trial participants in functional in vitro assays.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers that all aspects related to clinical pharmacology have been well addressed by the applicant.

Final study reports from pivotal studies COV001, COV002, COV003 and COV005 will be submitted no later than May 2022 and are subject to a specific obligation laid down in the MA (section 4).

Recommendations for further pharmacology development to be conducted post-approval are detailed in section 4, Annex I.

2.5. Clinical efficacy

The four studies COV001, COV002, COV003, and COV005 were pooled to support the efficacy and safety of this vaccine. For an individual study to be included in the pooled analysis of efficacy, a minimum of 5 primary endpoint defined cases had to be accrued. As a result, the interim efficacy analysis was pooled across phase 2/3 trials COV002 and COV003 only. Data from studies COV001 and COV005 (Phase 1/2) were only included in the immunogenicity and safety analyses. Therefore evidence of immunogenicity and safety for AZD1222 is based on pooled data from all 4 studies.

For all trials, the dose of 5×10^{10} vp AZD1222 (corresponding to not less than 2.5×10^{8} infectious units) was chosen for the clinical program based on data from other ChAdOx1 vectored vaccines expressing

different inserts. The initial intent of this programme was to implement a one dose only immunization schedule. Nonetheless, when it became apparent, following review of immunogenicity data from COV001, that a second dose provided increased immunogenicity, a decision was made to use a two-dose schedule. Thus, 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 least 4 weeks after the first dose. As a result of logistical constraints, 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 be at least 4 weeks) actually ranged from 3 to 23 weeks, i.e. 21 to 159 days (data on file).

In addition, due to a potency miscalculation of some batches, some subjects in trial COV002 (1716 participants) received a first dose that corresponded to half the amount (called low dose -LD- approximately 2.2×10^{10} vp) of the intended dose (called standard dose – SD- 5×10^{10} vp).

The manufacturing process evolved during the development programme. Different batches from different production processes were used throughout the clinical trials as follows: 1) Process 1 for Study COV001; 2) Process 2 for Studies COV002, COV003, and COV005; and 3) 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.

Batches had varying levels of viral particles per dose as determined by the AEX method, however mostly in the range of 3.5 - 6.0 x 10^{10}.

2.5.1. Main studies

Study COV001

This is a Phase I/II, single-blinded, controlled, individually randomised study in healthy adults aged 18-55 years recruited in the UK. AZD1222 or active control (licensed MenACWY) were administered via an intramuscular injection. The study aimed to assess efficacy, safety and immunogenicity of AZD1222. There were several groups in this study with the aim to test different number of doses and interval between doses.

The recruitment started on April 23, 2020 and enrolled 1077 healthy volunteers aged 18-55 years. Subjects were randomized to investigational vaccine (AZD1222) or MenACWY in a 1:1 pattern, and the trial staff administering the vaccine were not blinded to the vaccine to be administered and thus this is a single-blinded trial.

Baseline characteristics of participants were well balanced between AZD1222 and control groups. Males and female proportions were near 50%, and the participants were mainly white (91%). In this FIH trial, subjects seropositive to SARS-CoV-2 at baseline were excluded.

The study started as a Phase I and developed into a Phase II study. Initially it was designed as a one-dose study but after the analysis of the early immunogenicity cohorts, a result of robust booster responses was identified and the protocol was amended, resulting in the Phase II part of the study being carried out with two doses.

Regarding the outcomes of this study, the immunogenicity results obtained have been discussed in the Pharmacology section. The endpoint aimed to assess prevention of COVID-19 disease was not analysed. The study COV001 was originally planned to contribute to pooled interim analysis for efficacy. However, this study

was not included in it since it did not meet the predetermined criterion of at least 5 cases of COVID-19 at the time of this first interim analysis.

Study COV002

This is a Phase 2/3, participant-blinded individually randomized controlled trial in adults and healthy children in the UK, administering either a single dose or two-doses of AZD1222 or licensed MenACWY vaccine via IM injection. Additionally, to the healthy adults aged ≥18 years of age, this study was planned to include healthy children aged 5-12 YOA and HIV positive adults aged 18-55 YOA. However, a paediatric group was never enrolled; a separate trial will be conducted in children. Participants were blinded to the treatment arm they were allocated to. The trial staff administering the vaccine was not blinded. Vaccines were prepared out of sight of the participant and syringes were covered with an opaque object/material until ready for administration to ensure blinding.

Enrolment commenced after review of all available data from animal studies and at least 4 weeks safety and immunogenicity data DSMB reviewed from the first 54 participants receiving AZD1222 in COV001. The study began on May 28, 2020, and enrolled participants in 19 sites in the UK. Enrolment particularly targeted individuals working in professions with potentially higher risk of exposure to SARS-CoV-2, such as health and social care settings.

Pregnant women and subjects with severe and/or uncontrolled diseases (cardiovascular, respiratory, gastrointestinal, liver, renal, endocrine and neurological) were excluded but subjects with mild/moderate well controlled comorbidities were allowed.

The study is comprised of 12 main study groups (Groups 1-12), with an overall sample size of 12,390 participants. The study included subjects distributed in the following sequential age escalation/de-escalation immunogenicity sub studies:

1. Healthy adults aged between 56 – <70 years
2. Healthy adults aged 70 years or older
3. Healthy adults aged 18 – 55 years
4. HIV positive adults aged 18 – 55 years.

The intention of the trial was to test vaccines produced in different manufacturing sites in different age groups and assess potential differences in safety, reactogenicity and immunogenicity profiles. Of these, Groups 4 and 6 (adults aged 18 - 55 years), 9 (adults aged 56-69 years), and 10 (adults aged 70 years and older) are the main groups for evaluating efficacy in each age group. Only participants in groups 4, 6, 9 and 10 were advised to take prophylactic paracetamol for 24 hours (1000 mg every 4-6 hours) from the time of vaccination to reduce the likelihood of fever.

Group 11 was added as an open-label and not randomised group to investigate the impact of previous ChAdOx1 vectored vaccines on immune responses elicited by AZD1222.

The primary objectives were to assess efficacy (COVID-19 cases confirmed by PCR) and safety of the candidate AZD1222 against COVID-19 in adults aged 18 years and older. The secondary objectives were aimed at evaluating the humoral and cellular immunogenicity of AZD1222.

Conduct of the study: There have been many amendments to the study protocol. Important amendments include inclusion of additional dose groups, changes in swabbing criteria and clarification of primary endpoint,

the inclusion of two doses to all participants (instead of having a one-dose cohort and a two-dose cohort), increases in sample size, changes in eligibility criteria, and finally a decision to conduct a pooled analysis.

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. The cause of the miscalculation was the interference of an excipient, polysorbate 80 (PS80), with the spectrophotometry assay. The intended AZD1222 dosing regimens to be evaluated for efficacy was a SD/SD 2-dose regimen. However, due to the difference in concentration determination between the 2 analytical methods, some participants received a lower dose of approximately 2.2×10^{10} vp instead of the planned dose of 5×10^{10} vp. The study protocol was then amended to group the participants who received this LD/SD regimen separately for efficacy evaluation (Group 4). A reduced concentration (LD) was administered as Dose 1 to 1716 participants in Group 4.

Outcomes: Immunogenicity results from this trial have been described in section 2.4. The primary efficacy endpoint (PCR positive symptomatic COVID-19) was not analysed for this trial. Instead, subjects from groups 4, 6, 9, and 10, which included the largest number of subjects, were included in the pooled efficacy analysis discussed later (section 2.5.2).

Study COV003

This is a phase III, controlled, randomized, single-blind study which is ongoing in adults 18 years of age and older with high exposure to COVID-19 (mainly health-care workers), who are administered two-doses of AZD1222 or MenACWY and saline placebo by means of an IM injection with co-administered paracetamol. This study was initiated in June 2020 and 10,002 participants were recruited in Brazil. This study includes subjects with stable pre-existing health conditions.

Before the start of COV003 study, studies COV001 and COV002 were initiated in the UK. After the immunogenicity results of the COV001 UK phase 1/2 study showed higher levels of neutralizing antibodies with a prime-boost schedule, a booster dose of the vaccine was offered to all study participants. The protocol was amended correspondingly in July 2020.

Regarding inclusion criteria, participants enrolled before version 4.0 of the protocol needed to have negative serology by SARS-CoV-2 IgG antibodies. From version 4.0 onwards, this criterion did not apply.

As happened with study COV002, this study was originally planned as a standalone efficacy trial. After consulting with regulatory authorities, it was decided that the data from COV003 Phase 3 (Brazil) study would be analysed together with data from COV002 Phase 2/3 study in a pooled efficacy analysis. Therefore, the participant flow, baseline data and numbers analysed were assessed together in the pooled efficacy analysis and not individually for each study.

Study COV005

This is an ongoing adaptive phase 1/2 randomized, double-blinded, placebo-controlled trial to determine safety, immunogenicity and efficacy of AZD1222 vaccine in South African adults aged 18-65 years living without HIV, and safety and immunogenicity in adults living with HIV. For this study, 2,096 participants were recruited.

Regarding efficacy outcomes, no results are presented in this MAA. This study is not included in the pooled interim analysis for efficacy as it did not meet the predetermined criterion of at least 5 cases of COVID-19.

The reason why studies COV001 and COV005 did not have 5 COVID-19 cases despite having recruited 1077 and 2013 subjects, respectively, was investigated. Study COV001 recruited a low risk population. The healthy, low risk population recruited with reduced follow-up time clarifies why there have been such a low number of confirmed cases in this study. In study COV005, there were an sufficient number of cases by the time of the interim pooled analysis (DCO 4 November) because it started well after the other studies. In addition, a low baseline incidence of COVID-19 during key trial periods also played a role.

2.5.2. Pooled efficacy analysis

Only Studies COV002 and COV003 were pooled for the efficacy analysis supporting this MAA.

Studies COV002 and COV003 have several aspects in common that made them suitable for pooling. Both studies enrolled adults older than 18 years of age and inclusion and exclusion criteria were generally similar across studies. Participants received either AZD1222 or an active control without expected efficacy against SARS-COV-2. In trials in which a licensed MenACWY vaccine was administered the trial staff administering the vaccine were not blinded to the vaccine to be administered. Subjects seropositive to SARS-CoV-2 at baseline were also included.

The pooled efficacy data is mostly based on the final data cut of 7 December 2020. For some analyses, these data were not yet available at the time of assessment, in which case the interim data from 4 November 2020 is shown as indicated throughout the report.

Studies COV001 and COV005 were not included in the pooled analysis for the purpose of this MAA, as mentioned above because for both studies the predetermined criterion of at least 5 cases of COVID-19 was not met at the time of the pooled interim analysis for efficacy (DCO 4 November). For study COV005, 5 cases were determined following the adjudication process for the primary analysis at the time of the second data cut off (7 December DCO), and thus also this study was included in the pooled analysis, however these data could not be assessed for the purpose of this MAA due to the late availability, and will be considered post-authorisation.

In addition, at the time this report was finalised, a full set of data from all studies with a 7 December cut off was published (Voysey et al.). These data were not yet available in full at the time this MA was discussed (or could not be fully assessed, see for Study COV005 above) and are requested to be submitted via specific obligation in the context of the conditional MA (see section 4) for post-authorisation assessment.

Methods

Study Participants

All studies enrolled adults 18 to 55 year of age. In addition, Studies COV002 (UK, Phase 2/3) and COV003 (Brazil, Phase 3) enrolled older adults in age escalation groups of 56 to 69 years of age and ≥ 70 years of age. Enrolment in COV001 (UK, Phase I/II) was restricted to healthy adults. The other studies allowed the inclusion of people with underlying health conditions with the exception of severe and/or uncontrolled underlying disease. Pregnant and breastfeeding women subjects with a confirmed or suspected immunosuppressive or immunodeficiency state, subjects with a history of serious allergies, subjects with a known history of laboratory confirmed COVID-19 were excluded in all studies. The safety and immunogenicity of AZD1222 in adults with known HIV infection (on anti-retroviral treatment for at least three months and

HIV-1 viral load is <1,000 copies/ml within two weeks of randomization) was specifically investigated in a small subset of participants in Studies COV002 and COV005.

Treatments

Across the 4 University of Oxford-sponsored studies, participants were randomized to receive a single dose or two doses of either AZD1222, ranging from 2.2 to 5.0 × 10^{10} vp, or control. AZD1222 CTM was sourced from: 1) CBF at the University of Oxford; 2) Advent, Italy, and 3) Cobra Biologics. For control, the MenACWY vaccine was administrated in Studies COV001, COV002, and the first dose of COV003, and 0.9% normal saline (0.9% NaCl) was administered in Study COV005 and the second dose of Study COV003 for participants who received two doses.

The exposure information including dose level (i.e., SD [only for analysis set based on Dose1 SD], LD/SD, SD/SD), number of dose(s), all available dose schedule for two doses and further categorized dose schedule (< 6 weeks, 6-8 weeks, 9-11 weeks, 12+ weeks) was summarized by treatment for overall and each study (exploratory analyses).

Objectives

Primary Objective: To estimate the efficacy of 2 IM doses of AZD1222, with the second dose being SD, compared to control for the prevention of COVID-19 in adults ≥ 18 years of age.

Secondary Objectives of the Pooled Analysis:

- To evaluate the efficacy of AZD1222 against severe COVID-19 disease.
- To assess the safety, tolerability and reactogenicity profile of AZD1222.
- To assess humoral immunogenicity of AZD1222 if data are available.
- To assess the cellular immunogenicity of AZD1222 if data are available.

Of note, the original primary objective has been changed while the trials were ongoing, the initial intent was to implement a one dose only immunization schedule.

Outcomes/endpoints

Case definitions

All data from participants with SARS-CoV-2 virologically positive results from RT-PCR or other nucleic acid amplification tests will be assessed by a blinded adjudication committee and the events adjudicated as symptomatic-primary events will be used for all analyses. WHO clinical progression scale (WHO et al 2020), also determined by the adjudication committee, will be utilized to assess the severity of disease. The description of WHO clinical progression scale is in Table 14.

The case definition for evaluation of efficacy based on adjudicated results is defined as in Table 13.

Table 13: Case Definition for Evaluation of Efficacy

Case	Definition
COVID-19 (Primary) Virologically-confirmed[a] symptomatic cases of COVID-19	PCR-confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.
COVID-19 Severe Disease	WHO grade ≥ 6[b]
COVID-19 Hospital Admission	WHO grade ≥ 4[b]
COVID-19 Requiring ICU	WHO grade ≥ 7[b]
COVID-19 Death	WHO grade = 10[b]
Asymptomatic SARS-CoV-2 infection	PCR-confirmed SARS-CoV-2 infection and no symptom recorded in data. Confirmed by adjudication committee.
Asymptomatic or Unknown symptoms SARS-CoV-2 infection	PCR-confirmed SARS-CoV-2 infection, and no symptom recorded in data or symptoms unknown. Confirmed by adjudication committee.

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

Definition of Asymptomatic SARS-CoV-2 infection is: Virologically confirmed SARS-CoV-2 infection and no symptom record in data. Confirmed by adjudication committee.

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

In study COV005, a different case definition was maintained than the definition provided above, and cases with other symptoms than those noted above (e.g. diarrhoea, runny nose) could also have been included, which may have complicated interpretation of the pooled analysis if this study would have been included in the pooled analysis. The case adjudication process was put in place to classify cases to the case definition common to the pooled analysis

Table 14: WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy[a]	4
	Hospitalised; oxygen by mask or nasal prong	5
Hospitalised: severe disease	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO2/FiO2 ≥ 150 or SpO2/FiO2 ≥ 200	7
	Mechanical ventilation pO2/FIO2 < 150 (SpO2/FiO2 <200) or vasopressors	8
	Mechanical ventilation pO2/FiO2 < 150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

[a] If hospitalised for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; FiO2 = fraction of inspired oxygen; NIV = non-invasive ventilation; pO2 = partial pressure of oxygen; SpO2 = oxygen saturation.
Source: (WHO et al 2020).

Tests used for PCR confirmation of COVID-19 cases

In relation to the PCR methodology used to confirm COVID-19 cases, the Applicant indicates that locally authorized and verified NAAT methods were utilized for the confirmation of virologic disease for symptomatic participants. In total, 21 different methods were used in ≥1 of the clinical studies. Nineteen methods were used in the UK studies (COV001 and COV002), 8 methods (two of them were "Laboratory developed tests", 6 overlapped with the other studies) were used in Brazil and one method was used in South Africa (this method was also used in UK and Brazil). Moreover, the Applicant indicates that several laboratories in UK and Brazil performed the PCR testing. In the COV001 and COV002 studies, all testing laboratories were ISO 15189 accredited through UKAS. For the COV003 study, laboratories performing virologic testing were accredited through a combination of the Clinical Laboratory Accreditation Program (PALC), Brazil's Organização Nacional de Acreditação, National Quality Control Program - PNCQ (Brazilian Society of Clinical Analyzes - SBAC), and College of American Pathologists (CAP). This situation is far from optimal, i.e. using a single validated PCR test (with high specificity and sensitivity) and all samples being tested in one Central Lab. In order to clarify whether all the cases were diagnosed in a homogeneous manner, updated information as of 15 January 2021 was provided on the sensitivity, specificity, and validation status of all the PCR methods used in the clinical studies indicating that all methods have comparable sensitivity and specificity. Although not all validation reports are available, the remaining information can be submitted as a post-authorisation commitment. The information provided indicates that the integrity of the study has not been compromised.

Moreover, even if the overall sensitivity were imperfect, vaccine efficacy estimates would generally not be biased. Vaccine efficacy estimates may be overestimated if a PCR test with lower sensitivity is used more often for diagnosis of suspected cases in the AZD1222 arm than in the control arm, or if a PCR with a lower specificity is more often used in the placebo arm, which in a blinded study is not expected.

Virologic confirmation of Symptomatic COVID-19 disease by RT-PCR.

Study participants who became symptomatic with at least one qualifying symptom (fever ≥37.8°C, cough, shortness of breath, anosmia, or ageusia) were instructed to come to study site for assessment of virologic disease. Nasal swabs (which may include nasopharyngeal swabs), nasal/throat swabs, or saliva samples were to be collected by trained study staff. Nasal and nasal/throat swabs were collected using CE marked devices containing viral transport media (VTM) or universal transport media (UTM). The collection of saliva specimens was allowed per protocol in studies COV001, COV002, and COV005, but as of 14 December 2020, no saliva specimens had been collected.

Primary efficacy endpoint

The primary efficacy endpoint was the incidence of COVID-19 obtained by measuring the first case of SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥ 15 days post second dose of study intervention, with at least one of the following symptoms: objective fever (defined as ≥ 37.8°C), cough, shortness of breath, anosmia, or ageusia. Only cases with both the sampling date of positive PCR test (or other nucleic acid amplification test) and COVID-19 symptom(s) onset date ≥ 15 days post second dose were counted as events. For participants with multiple events, only the first occurrence was used for the primary efficacy endpoint analysis.

All PCR-positive results were assessed for the primary outcome, including those with symptoms swabbed by trial staff, those with positive throat swabs from weekly home-testing, and other potential sources of information such as health-care workers who are tested at their workplace as either a routine test procedure or due to developing symptoms.

For an individual study to be included in the pooled analysis of efficacy, a minimum of 5 primary endpoint defined cases were to be accrued.

The primary efficacy analysis was based on the SD/SD+LD/SD Seronegative for Efficacy analysis set. As discussed during scientific advice, performing an analysis on both the SD/SD and LD/SD regimes could also have been acceptable, provided however comparable immunogenicity was demonstrated, as including LD/SD would likely lead to a conservative estimate of efficacy.

Sensitivity and supportive analyses

As sensitivity of the primary analysis, a Cox Proportional Hazards model using the same covariates as for the primary analyses was run, and Kaplan-Meier curves were constructed.

The pooled analyses for the primary endpoint were repeated for participants who received two SDs of vaccine (i.e., SD/SD Seronegative for Efficacy analysis set) by study and overall.

Secondary Objectives of the Pooled Analysis

As secondary endpoints the sponsor have analysed the VE of AZD1222 against:

- Development of a severe COVID-19 disease,
- Hospital admission
- COVID-19 ICU requirement
- COVID-19 death
- After first dose

- Asymptomatic SARS-COV-2 infection.
- Asymptomatic or unknown symptoms of SARS-COV-2 infection.

Every topic has been assessed in the following data set:

- ≥ 15 Days Post Second Dose of Study Intervention for
  - LD/SD+SD/SD, seronegative
  - SD/SD, seronegative
  - LD/SD, seronegative
- Post First Dose of Study Intervention
- ≥ 22 Days Post First Dose of Study Intervention
  - Dose 1 SD, seronegative
  - Dose 1 LD, seronegative

Other secondary endpoints were:

- To assess the safety, tolerability and reactogenicity profile of AZD1222.
- To assess humoral immunogenicity of AZD1222 if data are available.
- To assess the cellular immunogenicity of AZD1222 if data are available.

Immunogenicity endpoints: see section 2.4.3.

Analysis populations

Analysis sets for the pooled and interim analyses are defined in the next Table 15.

Excluded from all analysis sets were groups/participants meeting any of the conditions below:

- Groups without randomization (e.g. group 3 of COV001, group 11 of COV002);
- Participants previously vaccinated with a ChAdOx1 vectored vaccine (group 11 of COV002);
- Participants with HIV diagnosed at study start (group 3 of COV005 and group 12 of COV002).

Participants who did not fulfil the requirements for re-vaccination with the booster dose did not receive a booster/second dose, including subjects with relevant adverse events, an anaphylactic reaction or pregnancy.

The relevant populations for analysis of the efficacy are shown in the next Table 15.

Table 15: Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the studies, to be used for reporting disposition and screening failures.
Any Dose for Safety Analysis set	All participants receiving at least one LD or SD of AZD1222 or the corresponding treatment in the control group
Any Dose for Efficacy	All participants in Any Dose for Safety, but for groups in COV002, only efficacy groups (i.e. groups 4, 6, 9,10) will be considered. This analysis set will be used for efficacy analysis.
Dose1 SD Seronegative for Efficacy	Only participants seronegative at baseline in Any Dose for Safety who received SD as the first dose of AZD1222 or in corresponding control group, and remain on-study 22 days after their first dose without having had a prior SARS-CoV-2 virologically-confirmed[a] COVID-19 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9,10) will be considered. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for efficacy analysis.
SD/SD + LD/SD Seronegative for Efficacy	Only participants seronegative at baseline in Any Dose for Safety who received LD/SD or SD/SD or in the corresponding control group, and remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 virologically-confirmed[a] COVID-19 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9,10) will be considered. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for the efficacy analysis.
SD/SD + LD/SD Seronegative ITT for Efficacy	Only participants seronegative at baseline in Any Dose for Safety who received two doses, planned to receive LD/SD or SD/SD or in the corresponding control group, and remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 virologically-confirmed[a] COVID-19 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9,10) will be considered. Participants will be analysed according to their randomized treatment irrespective of whether they have prematurely discontinued, according to the intent-to-treat principle. This analysis set will be used for the sensitivity analysis of primary endpoint.

Table 15: Populations for Analysis

Population	Description
SD/SD Seronegative for Efficacy	Only participants seronegative at baseline in SD/SD + LD/SD Seronegative for Efficacy analysis set who received SD/SD or in the corresponding control group, and remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 virologically-confirmed[a] COVID-19 infection. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for the efficacy analysis.
LD/SD Seronegative for Efficacy	Only participants seronegative at baseline in SD/SD + LD/SD Seronegative for Efficacy analysis set who received LD/SD or in the corresponding control group, and remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 virologically-confirmeda COVID-19 infection. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for the efficacy analysis.
Dose1 LD Seronegative for Efficacy	Only participants seronegative at baseline in Any Dose for Safety who received LD as the first dose of AZD1222 or in corresponding control group, and remain on-study 22 days after their first dose without having had a prior SARS-CoV-2 virologically-confirmed[a] COVID-19 infection. In addition, for groups in COV002, only efficacy groups (i.e., groups 4, 6, 9,10) will be considered. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for efficacy analysis.

[a] Virologically-confirmed from RT-PCR or other nucleic acid amplification test.
ITT = intent-to-treat; LD = low dose; RT-PCR = reverse transcriptase-polymerase chain reaction; SD = standard dose.

Definitions of Subgroups

To explore the implications for efficacy, safety, and immunogenicity among different populations, the following subgroups were used:

- Age at randomization:
  - 18-64, 65 years and above
  - 18-55, 56-69, 70 years and above
- Country (UK, Brazil vs South Africa)
- Comorbidity at baseline (at least one comorbidity vs. no comorbidity), where comorbidity is BMI ≥30 kg/m2 at baseline, Cardiovascular Disorder, Respiratory disease or Diabetes.
- Baseline serostatus (seronegative vs seropositive).

The analyses by each subgroup were performed for all endpoints (efficacy, safety, and immunogenicity) unless specified otherwise. Regarding age, there was no formal stratification for age in all trials. Only in

studies COV002 and COV003, participants were randomised by age as mentioned above and subgroup analyses were planned for these age groups only. COV001 and COV002 enrolled only individuals aged 18-55YOA and 18-65YOA respectively.

Additional subgroups that may be explored include but are not limited to:

- Gender (male, female)
- Race (Asian, Black, White, Mixed, Other, Unknown): only categories with at least 100 individuals exposed will be presented
- Use of prophylactic paracetamol (for analysis of reactogenicity)
- Dose level (LD/SD vs SD/SD)
- Dose schedule (< 6 weeks, 6-8 weeks, 9-11 weeks, ≥ 12 weeks)
- Control type (MenACWY, Saline) (for safety only).

Sample size

This was an event driven analysis in participants who received two doses, with a SD as the second dose (i.e., participants who received LD/SD or SD/SD). The initial plan was to combine the four studies into one pooled analysis. The primary analysis will be triggered when 105 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. This would provide 90% power for the 20% threshold to assume a true vaccine efficacy of 60%.

An interim analysis for efficacy will be triggered when 53 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 in pooled studies. This would provide 77% power for the 20% threshold to assume a true vaccine efficacy of 70%.

The planned 5% alpha will be split across the interim and primary analyses. A gamma Alpha-Spending function (gamma -2.5) is used to control the overall Type 1 Error at 5%. The planned alpha level is 1.13% for interim analysis and 4.44% for primary analysis.

The study is designed to show superiority with a superiority margin of 20%. The primary analysis was planned to be triggered when 105 cases were accrued over all four studies included in the pooling. Due to relatively low rate of accrual of cases, the total sample size was increased in various amendments of the original trial protocols, to reduce the duration of the trial.

Randomisation

The randomization for each of the 4 studies was stratified by study site and study group (not mentioned in the study protocols or SAPs). REDCap was used for COV001, COV002 and COV003 whereas randomization envelopes were used for COV005.

Participants were randomized concurrently to AZD1222 and control. Consequently the LD treated participants and SD treated participants had a concurrent control arm within each block and strata.

Blinding (masking)

The studies COV001, COV002 and COV003 were participant-blind and study COV005 was double-blind.

Participants were blinded to the vaccine they received as were the investigators and the clinical staff involved in assessing participants at study visits, or the staff who managed patient follow up. In addition, laboratory staff were blind. The only unblinded members of the Oxford team were IT programmers, data managers, statisticians, and vaccinating nurses.

Statistical methods

This interim pooled analysis was planned to be triggered when at least 53 cases of SARS CoV 2 virologically confirmed symptomatic COVID 19 that occurred ≥ 15 days post the second dose had been reported in participants who received SD/SD across the AZD1222 and control groups in pooled studies. The Health Authorities have accepted the testing strategy for this pooled interim analysis although noted this was not the ideal approach and the derived uncertainties will need careful evaluation. Due to the rapid accumulation of cases prior to database cut-off, 131 events were included in the analysis, of which 98 were in participants that received the SD/SD regimen.

In the context of the CHMP scientific advice, the primary analysis was planned to be triggered when 105 COVID-19 cases (SARS-CoV-2 virologically confirmed) that occurred ≥ 15 days post the second dose had been reported in participants who received SD/SD across the AZD1222 and control groups. The analysis will include participants who received two doses, with the second dose being SD (i.e., participants who received LD/SD or SD/SD).

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 SD/SD). Whilst alpha was determined based on the 98 cases from participants who received SD/SD, the primary interim analysis was prespecified to include participants who received ether SD/SD or LD/SD (131 cases).

A Poisson regression model with robust variance (Zou 2004) will be used as the primary efficacy analysis model to estimate the relative risk (RR) of the incidence of SARS-CoV-2 virologically-confirmed primary symptomatic COVID-19 between the AZD1222 and control groups. The model contains the term of study code, treatment group, and age group at randomization (i.e., 18-55 years, 56-69 years, and ≥ 70 years). The logarithm of the period at risk for primary endpoint for pooled analysis will be used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occur. Vaccine efficacy (VE), which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group expressed as a percentage, will be calculated as VE = 1- relative risk. For the primary endpoint efficacy objective to be met, the lower bound of the CI for the vaccine efficacy must be > 20%. A 95.84% CI is used for the primary endpoint in the SD/SD + LD/SD Seronegative for Efficacy Analysis Set, as well as the corresponding SD/SD seronegative efficacy analysis populations. All remaining efficacy analyses used a 95% CI.

The analyses for the primary endpoint for the pooled analysis will be repeated for participants who received two SDs of vaccine (i.e., SD/SD Seronegative for Efficacy analysis set) for each study.

As sensitivity analysis for the primary analysis, a Cox Proportional Hazards model using the same covariates as for the primary analyses as well as Kaplan-Meier curves will be 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.

Time to event, i.e., the duration in days since 15 days post second study dose to event or censoring, will be fit using the PH model with treatment as a factor and age group and country as stratum. Hazards ratios for each study arm along with the two-sided (1 ɑ) % CI will be obtained from the PH model.

In general, the secondary efficacy analysis will be conducted in a similar manner as described above for the primary efficacy endpoint.

Calculation of study days

Study Day contains the number of days after an event. Reference start date is defined as the day of the first dose of study drug intervention i.e., Day 0. Study Day will be computed as follows:

Study Day = (Date of event –Date of first dose of study drug).

In addition, day relative to vaccination will be derived for each vaccination dose. For example, day relative to the first dose will be equal to the Study Day. Day relative to the second dose will start with a value of 0 on the day of the second dose.

Missing data

Missing data values were not imputed unless otherwise specified.

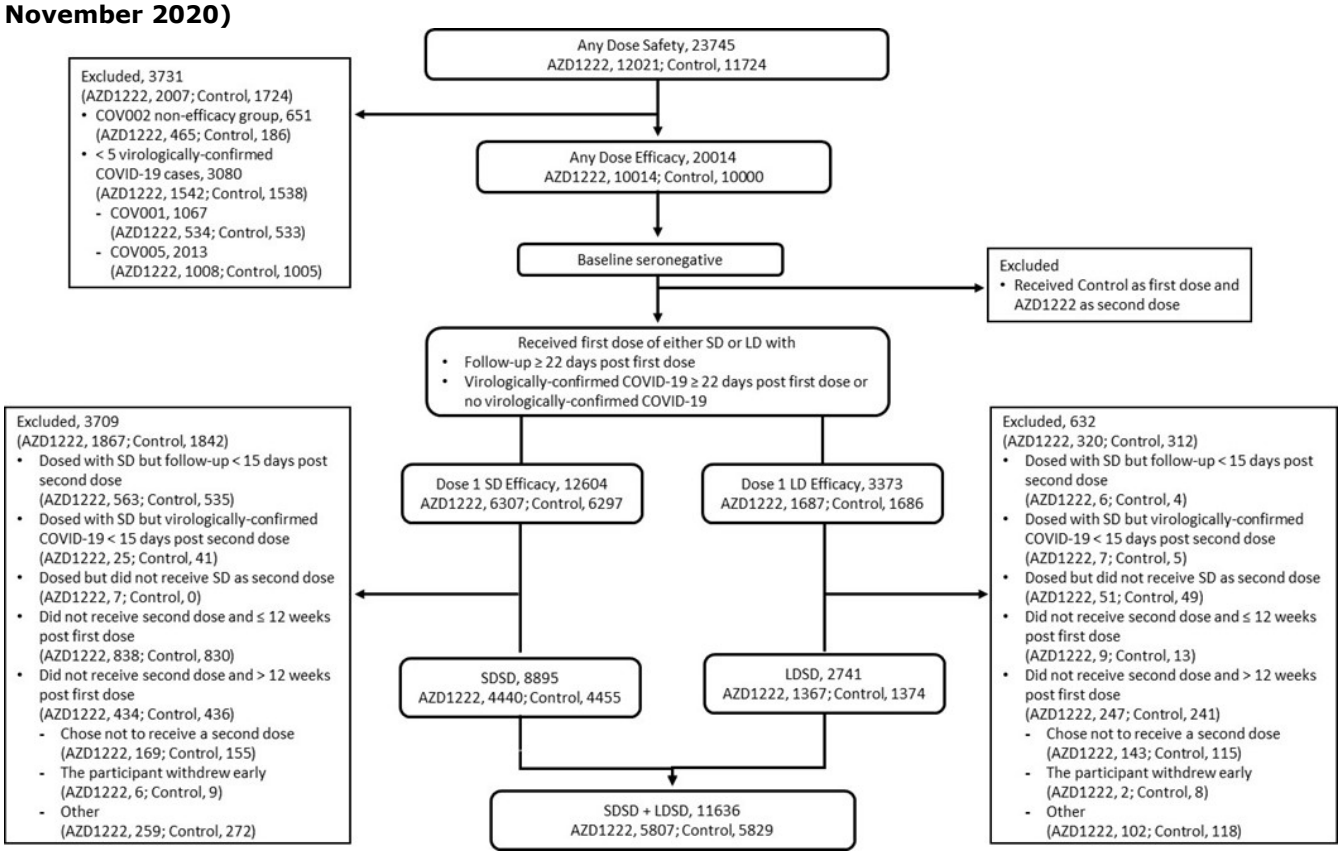
Results

Although by the time this assessment was conducted the main analysis were updated based on the data cut off of 7 December, some outcomes were not yet available and thus some results presented in this report are still based on the first data cut off of 4 November. The data cut off (DCO) is specified in each table. The full set of results based on the second data cut off 7 December is requested as specific obligation (see section 4) and will be assessed post-authorisation.

Participant flow (data cut off 04 November 2020)

Figure 3 presents a flow chart for the disposition of participants in the efficacy analysis sets.

Figure 3: Disposition of Participants for the Efficacy Analysis Sets (AZD1222 Pooled Analysis, 04 November 2020)



As can be seen in the next Table, only 100 participants from a total of 20,014 in the any dose efficacy set discontinued, and these numbers were well balanced between the AZD1222 and the Control group.

Table 16: - Participant disposition (All participants analysis set) (DCO 04 November 2020)

	Number (%) of Participants		
	AZD1222	**Control**	**Total**
Participants in Any Dose for Efficacy Analysis Set	10014 (83.3)	10000 (85.3)	20014 (84.3)
Ongoing in study	9968 (82.9)	9946 (84.8)	19914 (83.9)
Completed study	0	0	0
Discontinued early from study	46 (0.4)	54 (0.5)	100 (0.4)
Reason for discontinuing early from study			
Adverse Event	0	1 (<0.1)	1 (<0.1)
Death	1 (<0.1)	2 (<0.1)	3 (<0.1)
Exclusion Criteria Met	0	1 (<0.1)	1 (<0.1)
Lost To Follow-Up	6 (<0.1)	8 (0.1)	14 (0.1)
Other	10 (0.1)	11 (0.1)	21 (0.1)
Withdrawal By Subject	29 (0.2)	31 (0.3)	60 (0.3)

Moreover, further information on the numbers of subjects excluded from the LD/SD+SD/SD efficacy set are shown in Table 17.

Table 17: Participant Disposition (SDSD+LDSD seronegative for efficacy analysis set) (DCO 04 November 2020)

	Number (%) of Participants		
	AZD1222	Control	Total
Participants in SDSD + LDSD Seronegative for Efficacy Analysis Set	5807 (48.3)	5829 (49.7)	11636 (49.0)
Ongoing in study	5804 (48.3)	5822 (49.7)	11626 (49.0)
Completed study	0	0	0
Discontinued early from study	3 (<0.1)	7 (0.1)	10 (<0.1)
Reason for discontinuing early from study			
Adverse Event	0	1 (<0.1)	1 (<0.1)
Other	1 (<0.1)	3 (<0.1)	4 (<0.1)
Withdrawal By Subject	2 (<0.1)	3 (<0.1)	5 (<0.1)
Participants not in SDSD + LDSD Seronegative for Efficacy Analysis Set	6214 (51.7)	5895 (50.3)	12109 (51.0)
Reason not in SDSD + LDSD Seronegative for Efficacy Analysis Set			
Dosed but did not receive SDSD or LDSD	4031 (33.5)	3842 (32.8)	7873 (33.2)
COV002 non-efficacy group	465 (3.9)	186 (1.6)	651 (2.7)
Not seronegative at baseline	576 (4.8)	585 (5.0)	1161 (4.9)
Dosed with two doses with followup <15 days post second dose	664 (5.5)	620 (5.3)	1284 (5.4)
Virologically-confirmed COVID-19 prior to 15 days post second dose	30 (0.2)	45 (0.4)	75 (0.3)
Less than 5 primary endpoint defined cases in study	1542 (12.8)	1538 (13.1)	3080 (13.0)
Received first dose as Control and second dose as AZD1222	5 (<0.1)	0	5 (<0.1)

SD = Standard dose; LD = Low dose.
Unless otherwise specified, denominator used in the percentage calculation is the number of participants in Any Dose for Safety Analysis Set.
Reasons not in specific analysis set may not be mutually exclusive.
[a] Participants signed the informed consent.
[b] Denominator is the number of participants screened.
[c] Summarized based on randomized treatment.

/SASDATA/cars/prod/d811/pooled/maasubmission1/tables/t_disp.sas (/SASDATA/cars/prod/d811/pooled/maasubmission1/tables/t_disp.rtf) 03DEC2020 23:45

Upon request, the Applicant clarified why many subjects (33.5%) did not receive the second dose: in all studies, the common reasons for not receiving a second dose mostly involved the design features of the study with a number of amendments being made in response to evolving data in the early stages of this fast moving clinical programme. For example, as can be seen in the next figure for trial COV003, the reason included being in a single dose group without an option for a second dose, being in a single dose group and having not yet responded to the option of an optional second dose, or being in a single dose group and declining an optional second dose. It should be noted that participants were reconsented for administration of a second dose and some subjects opted out while others had not responded by the time of the data cut off. "Other" includes, for example, participants who became ineligible for a second dose (e.g. new exclusionary medical condition).

Table 18: Overview of COV003 Participants Not Receiving the Second Vaccination (Any Dose for Safety Analysis Set) (DCO 04 November 2020)

	N (%) of Participants		
	AZD1222 (N=5000)	Control (N=5002)	Total (N=10002)
Participants that did not receive the second vaccination	2436 (48.7)	2505 (50.1)	4941 (49.4)
Reason:			
Participants had the second vaccination visit but vaccination form did not indicate complete	4 (< 0.1)	4 (< 0.1)	8 (< 0.1)
Participants enrolled in the single dose group and have not responded to the second dose option	1390 (27.8)	1415 (28.3)	2805 (28.0)
Participants enrolled in the single dose group and declined the optional second dose	25 (0.5)	26 (0.5)	51 (0.5)
Follow-up ≤ 12 weeks post first dose by 4 Nov 2020	996 (19.9)	1036 (20.7)	2032 (20.3)
Follow-up > 12 weeks post first dose by 4 Nov 2020	21 (0.4)	24 (0.5)	45 (0.4)
The participant withdrew early	1 (< 0.1)	0	1 (< 0.1)
Other	20 (0.4)	23 (0.5)	43 (0.4)

Source: Supplemental Table IEMT99.1

Recruitment

Patients were enrolled between April 23 and 08 December 2020 (COV002 Last Patient Enrolled was 08Dec2020; for COV003 last patient enrolled was 01Dec2020). The data cut off for the interim analysis was 4 November 2020. The data cut off for the primary analysis was 7 December. Studies are still ongoing. Study COV002 was conducted in 19 centres the UK, and study COV003 in six centres Brazil.

Conduct of the study

Changes in the protocol before database lock

Several changes have been made to the protocol while the studies were conducted. For COV001 there were 12 revisions of the protocol, for COV002 14 revisions, for COV003 8 revisions and for COV005 4 revisions. Major changes related to increases in sample size and study groups, changes in inclusion and exclusion criteria, changes to swabbing criteria and clarifications around the primary endpoint, addition of a second dose, and finally the decision to conduct a pooled analysis. For the final analyses on the final data cut (DCO2: 07 December 2020) the primary case definition for virologically-confirmed symptomatic cases of COVID-19 was updated to include all PCR-confirmed SARS-CoV-2 events with WHO grade ≥ 4, regardless of presence of symptoms.

Protocol deviations

A summary of key points on protocol deviations in COV001, COV002, COV003 and COV005 is provided:

- Incomplete visits or visits out of window are common across the studies (and are not unexpected in clinical trials). These errors were compounded by both the clinical hold for safety (for example, second doses could not be given within the specified window) and the unique challenges faced by sites trying to undertake complex studies during either national lockdowns or partial closure of transport services due to COVID-19
- Sampling errors are common to sites across the programme but vary between site, study and individual case. No pattern could be identified that would suggest a systematic error in investigator training or a protocol issue
- Vaccine administration errors were seen with some individuals receiving the wrong type of vaccine relative to the arm they were randomised to. As unblinded pharmacists were drawing up active or control doses at their sites, based upon a randomisation schedule rather than central supplies of pre-prepared vaccine, this error is not unexpected. However, such errors were noted to be relatively infrequent
- Whilst informed consent deviations were seen across sites and studies, many of these were similar in nature within a site, and the frequency was driven by high daily recruitment rates, as any corrective action, even if implemented rapidly, took effect after many participants had been recruited.

The applicant considers that protocol deviations have been appropriately recorded, evaluated and addressed, both at the time and with subsequent formal corrective and preventative actions such as retraining or the broader use of CAPAs. Documentation has been in accordance with expected norms in ICH GCP, with the exception of COV005, where division into minor and major deviations is now ongoing.

Exposure to AZD1222

As of the data cut-off of 04 November 2020, 12,021 participants of the 4 studies included in the application have received at least one dose of AZD1222. Of these participants, 8,266 (68.8%) have received 2 doses of AZD1222 (Next Table). Overall, in the primary efficacy analysis set, approximately one-third of participants each had a dose interval in the range of < 6 weeks, 6 to 11 weeks, or ≥ 12 weeks (DCO 4 November 2020).

Table 19: **Exposure to Study Intervention at the time of data cut-off (04 November 2020)***

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

a Dose level of control group is decided by the dose level of corresponding vaccine group.
Total row includes the number of participants with non-missing data for the corresponding characteristic and was used as the denominator for calculating percentages for all categories.
***** data not available for these dosing intervals for SDSD seronegative for the 7 December 2020 DCO
Source data: Main Safety Tables 1.2.1.1 and 1.2.1.2

For the data cut-off date of 07 December 2020, the SD/SD seronegative for efficacy analysis set was based on the dosing intervals <4 weeks (<28 days), 4 to 12 weeks (≥28 to ≤84 days) and >12 weeks (≥85 days). Out of 6106 participants in the vaccine group, 5258 (86%) participants received the second dose in the 4 to 12 weeks interval (5210 in the control), 807 (13%) participants received the second dose less than 12 weeks after dose 1 (828 in the control), and 41 (0.7%) participants received the second dose less than 4 weeks after dose 1 (52 in the control). [Source IEMT table 206.3.1]

Participants who received the second dose in the 4-12 weeks interval had a median duration of follow up of 78 days since the second dose (min 17, max 127), and a median duration of follow up from the first dose of 118.0 days (min 45, max 182); participants in the control group in the same 4-12 weeks dosing interval had the same median duration of follow-up since the second dose as the vaccine group (78 days, same range) and 117 days since the first dose (min 45, max 182). [Source IEMT table 206.5.2]

Baseline data

The following Table details the demographics and baseline characteristics for the LD/SD, SD/SD and the LD/SD+SD/SD Seronegative for Efficacy Analysis Sets. Other characteristics of the population sets used for the Vaccine efficacy analysis follow in the next table.

Table 20: Selected Population Characteristics for LD/SD and SD/SD Seronegative Analysis Sets by Country (DCO 04 November 2020)*

Parameter	Statistic	LD/SD – UK		SD/SD – UK		SD/SD - Brazil	
		AZD1222 (N = 1367)	Control (N = 1374)	AZD1222 (N = 2377)	Control (N = 2430)	AZD1222 (N = 2063)	Control (N = 2025)
Age (years) at screening	Median	40.0	40.0	44.00	44.00	37.0	36.0
	≥ 65 years, n (%)	0	0	277 (11.7)	279 (11.5)	64 (3.1)	40 (2.0)
Race, n (%) ¥	White	1261 (92.2)	1296 (94.3)	2189 (92.1)	2238 (92.1)	1357 (65.8)	1366 (67.5)
	Other	8 (0.6)	7 (0.5)	14 (0.6)	12 (0.5)	260 (12.6)	260 (12.8)
Comorbidity, n (%)	Yes	459 (33.6)	463 (33.7)	852 (35.8)	935 (38.5)	759 (36.8)	735 (36.3)
	No	908 (66.4)	909 (66.2)	1524 (64.1)	1492 (61.4)	1301 (63.1)	1282 (63.3)
Dose interval (weeks)	Median	12	12	10	10	5	5
Dose interval n(%)	< 6 weeks	0	0	453 (19.1)	454 (18.7)	1249 (60.5)	1244 (61.4)
	6-8 weeks	6 (0.4)	6 (0.4)	317 (13.3)	277 (11.4)	245 (11.9)	244 (12.0)
	9-11 weeks	388 (28.4)	378 (27.5)	653 (27.5)	718 (29.5)	403 (19.5)	392 (19.4)
	≥ 12 weeks	973 (71.2)	990 (72.1)	954 (40.1)	981 (40.4)	166 (8.0)	145 (7.2)
Duration of FU post dose 1 (days)	Mean	-	-	118.3	118.3	97.0	96.9
Duration of FU since 15 days post dose 2 (days)	Mean	-	-	46.6	46.0	38.8	38.9

* data not available for the 7 December 2020 DCO

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

Table 21*:* Baseline characteristics (SD/SD Seronegative for Efficacy Analysis Set) per study and overall (DCO 04 November 2020)*

		UK		Brazil		Pooled	
		AZD1222 (N=2377)	**Control (N=2430)**	**AZD1222 (N=2063)**	**Control (N=2025)**	**AZD1222 (N=4440)**	**Control (N=4455)**
Body Mass Index (BMI) (kg/m2)							
	Mean, (min, max across studies and treatment arms: 11.4, 95.6)	26.4	26.5	26.4	26.5	26.4	26.5
	< 30 kg/m2	1908 (80.3)	1920 (79.0)	1635 (79.3)	1596 (78.8)	3543 (79.8)	3516 (78.9)
	>= 30 kg/m2	468 (19.7)	507 (20.9)	421 (20.4)	421 (20.8)	889 (20.0)	928 (20.8)
	Missing	1 (<0.1)	3 (0.1)	7 (0.3)	8 (0.4)	8 (0.2)	11 (0.2)
Serostatus at Day 0 n (%)							
	Negative	2377 (100)	2430 (100)	2063 (100)	2025 (100)	4440 (100)	4455 (100)
Cardiovascular Disorder at baseline n (%)**		264 (11.1)	266 (10.9)	271 (13.1)	244 (12.0)	535 (12.0)	510 (11.4)
	Hypertension	168 (7.1)	151 (6.2)	96 (4.7)	93 (4.6)	264 (5.9)	244 (5.5)
	Other	71 (3.0)	77 (3.2)	30 (1.5)	17 (0.8)	101 (2.3)	94 (2.1)
Respiratory disease at baseline n (%)***		285 (12.0)	317 (13.0)	215 (10.4)	211 (10.4)	500 (11.3)	528 (11.9)
	Asthma	239 (10.1)	270 (11.1)	60 (2.9)	53 (2.6)	299 (6.7)	323 (7.3)
	Other	39 (1.6)	39 (1.6)	8 (0.4)	6 (0.3)	47 (1.1)	45 (1.0)
Diabetes at baseline n (%)		58 (2.4)	60 (2.5)	59 (2.9)	60 (3.0)	117 (2.6)	120 (2.7)
Current smoker at baseline n(%)		115 (4.8)	139 (5.78)	108 (5.2)	114 (5.6)	223 (5.0)	253 (5.7)

* Individual trial data not available for the 7 December 2020 DCO. Source: Supplemental Tables in IEMT 106.1
** including Chronic heart failure, Ischaemic heart disease (including angina), Atrial fibrillation, Peripheral vascular disease, Valvular heart disease, Myocardial infarction, Hypertension, Other, Cardiovascular disorder with missing subcategory
*** including COPD, bronchiectasis, asthma, other and respiratory diseases missing subcategory

Based on Demographics and Baseline Characteristics (SDSD Seronegative for Efficacy Analysis Set, 4 to 12 Weeks Dosing Interval), DCO2 (07 December 2020), 13% of participants were ≥65 years of age with the maximum age being 88 years. Also, a small number of subjects (16.2%) from 56 to 69 YOA are included in this efficacy set and races other than "white" are poorly represented. The mean age was approximately 44 years old, approximately 55% were female, 76% of participants were White and 39.2 % of participants had a comorbidity at baseline.

Table 22:Demographics and Baseline Characteristics (SDSD Seronegative for Efficacy Analysis Set, 4 to 12 Weeks Dosing Interval), DCO2 (07 December 2020)

	Pooled (COV002 + COV003)	
	AZD1222 (N = 5258)	**Control (N = 5210)**
Age (years) at screening		
n	5258	5210
Mean	44.37	44.46
SD	15.22	15.18
Median	42.00	42.00
Min	18.0	18.0
Max	88.0	
Age group at screening, n (%)		
18 to 64 years	4572 (87.0)	4545 (87.2)
≥ 65 years	686 (13.0)	665 (12.8)
18 to 55 years	3934 (74.8)	3907 (75.0)
56 to 69 years	852 (16.2)	824 (15.8)
≥ 70 years	472 (9.0)	479 (9.2)
≥ 75 years	147 (2.8%)	not available
Sex, n (%)		
Female	2898 (55.1)	2888 (55.4)
Male	2360 (44.9)	2322 (44.6)
Transgender	0	0
Race [a], n (%)		
White	4005 (76.2)	4012 (77.0)
Asian	177 (3.4)	156 (3.0)
Black	335 (6.4)	334 (6.4)
Other	426 (8.1)	387 (7.4)
Mixed	305 (5.8)	312 (6.0)
Unknown	10 (0.2)	9 (0.2)
Body Mass Index (BMI) (kg/m^2)		
n	5230	5179
Mean	26.47	26.65
SD	4.874	4.986
Median	25.70	25.80
Min - Max	13.3 – 68.5	
BMI category, n (%)		
< 30 kg/m^2	4151 (78.9)	4085 (78.4)

Table 22:Demographics and Baseline Characteristics (SDSD Seronegative for Efficacy Analysis Set, 4 to 12 Weeks Dosing Interval), DCO2 (07 December 2020)

	Pooled (COV002 + COV003)	
	AZD1222 (N = 5258)	**Control (N = 5210)**
≥ 30 kg/m^2	1079 (20.5)	1094 (21.0)
Missing	28 (0.5)	31 (0.6)
Serostatus at Day 0, n (%)		
Negative	5258 (100)	5210 (100)
Cardiovascular Disorder, n (%)		
Yes	861 (16.4)	827 (15.9)
No	4397 (83.6)	4383 (84.1)
Chronic heart failure	2 (<0.1)	1 (<0.1)
Ischaemic heart disease (including angina)	24 (0.5)	14 (0.3)
Atrial fibrillation	14 (0.3)	20 (0.4)
Peripheral vascular disease	6 (0.1)	10 (0.2)
Valvular heart disease	9 (0.2)	19 (0.4)
Hypertension	643 (12.2)	612 (11.7)
Myocardial infarction	10 (0.2)	10 (0.2)
Other	153 (2.9)	141 (2.7)
Respiratory disease, n (%)		
Yes	575 (10.9)	539 (10.3)
No	4683 (89.1)	4671 (89.7)
COPD (including chronic bronchitis and emphysema)	9 (0.2)	13 (0.2)
Bronchiectasis	5 (0.1)	6 (0.1)
Asthma	362 (6.9)	352 (6.8)
Other	199 (3.8)	168 (3.2)
Diabetes, n (%)		
Yes	202 (3.8)	165 (3.2)
No	5056 (96.2)	5045 (96.8)
Type 1 Diabetes	12 (0.2)	8 (0.2)
Type 2 diabetes not using insulin	147 (2.8)	99 (1.9)
Type 2 diabetes using insulin	12 (0.2)	13 (0.2)
Other	31 (0.6)	45 (0.9)
Comorbidity at baseline [b], n (%)		
Yes	2068 (39.3)	2040 (39.2)
No	3174 (60.4)	3144 (60.3)

Table 22:Demographics and Baseline Characteristics (SDSD Seronegative for Efficacy Analysis Set, 4 to 12 Weeks Dosing Interval), DCO2 (07 December 2020)

	Pooled (COV002 + COV003)	
	AZD1222 (N = 5258)	**Control (N = 5210)**
Missing	16 (0.3)	26 (0.5)
Current smoker, n (%)		
Yes	251 (4.8)	288 (5.5)
No	5007 (95.2)	4922 (94.5)
Former Smoker, n (%)		
Yes	919 (17.5)	944 (18.1)
No	4088 (77.7)	3976 (76.3)
Missing	251 (4.8)	290 (5.6)

a Each race category counts participants who selected that category. Arab is counted under white.
b Comorbidities at baseline = Yes if any comorbidity (BMI ≥ 30 kg/m2 at baseline, cardiovascular disorder, respiratory disease or diabetes) is Yes.
Source: Supplemental Tables IEMT 206.1.1.2 (Demographics), IEMT 206.1.2.2 (Baseline Characteristics).

Numbers analysed

Table 23 presents the disposition of participants in the pooled analysis sets for efficacy, safety, and immunogenicity.

Table 23: Disposition of Participants in Pooled Analysis Sets (DCO 04 November 2020)*

Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	**Control**	**Total**
All participants randomized					12018	11735	23753
Safety							
Any Dose for Safety [a]	As treatment received	Pos and Neg and Missing	Any	From Dose 1	12021	11724	23745
Dose1 SD for Safety [a]	As treatment received	Pos and Neg and Missing	SD/SD SD single dose SDLD	From Dose 1	10069	9902	19971
Efficacy							
Any Dose for Efficacy [a]	As treatment received	Pos and Neg and Missing	Any	From Dose 1	10014	10000	20014
SD/SD + LD/SD Seronegative for Efficacy [b] (Primary population)	As treatment received	Seronegative	SD/SD LD/SD	From 15 days post Dose 2	5807	5829	11636
SD/SD + LD/SD Seronegative ITT for Efficacy [b]	As randomized	Seronegative	SD/SD LD/SD	From 15 days post Dose 2	5814	5831	11645
SD/SD Seronegative for Efficacy [b]	As treatment received	Seronegative	SD/SD	From 15 days post Dose 2	4440	4455	8895

Table 23: Disposition of Participants in Pooled Analysis Sets (DCO 04 November 2020)*

Analysis set	As randomized or as treatment received	Serostatus	Dosing regimens	Time period of observation	Number of participants		
					AZD1222	Control	Total
LD/SD Seronegative for Efficacy [b]	As treatment received	Seronegative	LD/SD	From 15 days post Dose 2	1367	1374	2741
Dose1 SD Seronegative for Efficacy [c]	As treatment received	Seronegative	SD/SD SD single dose SDLD	From 22 days post Dose 1	6307	6297	12604
Dose1 LD Seronegative for Efficacy [c]	As treatment received	Seronegative	LD/SD LD single dose LDLD	From 22 days post Dose 1	1687	1686	3373
Immunogenicity							
SD/SD + LD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SD/SD LD/SD	All available timepoints	1666	1205	2871
SD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	SD/SD	All available timepoints	1367	1031	2398
LD/SD for Immunogenicity [a]	As treatment received	Pos and Neg and Missing	LD/SD	All available timepoints	299	174	473

a Analyses on these sets use data starting from first dose.
b Analyses on these sets use data starting from ≥ 15 days post the second dose.
c Analyses on these sets use data starting from ≥ 22 days post the first dose.
LD = low dose; Neg = negative; Pos = positive; SD = standard dose.
* data not available for the 7 December 2020 DCO
Source: Main Safety Tables 1.1.1.1 and 1.1.1.2; Immuno Table 1.1.1.2

Outcomes and estimation

Adjudicated events

The tables below summarize the total number of cases adjudicated by presence of symptoms and various timeframes by study.

Table 24: Number of all first SARS-CoV-2 virologically-confirmed COVID-19 infection occurring from first dose of study intervention by presence of symptoms and time frame (Any Dose for Efficacy Analysis Set, Seronegative at Baseline for COV002, COV003)

Study and Time Frame	Total number of events	Events adjudicated as Symptomatic - Primary[a] adjudicated primary events		Events adjudicated as Symptomatic - non Primary[b]	
COV002		**AZD1222 (N=5371)**	**Control (N=5089)**	**AZD1222 (N=5371)**	**Control (N=5089)**
total events	172	46	104	11	11
≥15 days post second dose	140	18	68	6	10
COV003		**AZD1222 (N=4791)**	**Control (N=4797)**	**AZD1222 (N=4791)**	**Control (N=4797)**
total events	199	61	121	9	8
≥15 days post second dose	50	12	33	3	2

Data cutoff date: 04NOV2020 [Source Table IEMT63.2].
Data not available for the DCO 07 Dec 2020 at the time of writing this report.

[a] Case of COVID-19 with one of the following symptoms: objective fever (defined as >= 37.8 °C), cough, shortness of breath, anosmia, or ageusia and were considered as **adjudicated events**.

[b] Symptomatic case of not meeting case definition of COVID-19.

[c] No upper limit for participants who do not received the second dose.
The observation period for the endpoint was from the first dose up to data cut off or 1 year post the second dose.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.

Endpoints were adjudicated by a blinded endpoint adjudication committee. The endpoint adjudication committee (EAC) is part of The Jenner Institute. In total 9 events in the AZD1222 group and 12 events in the control group were judged by the adjudication committee to not fulfil the primary endpoint criteria. The analysis for the incidence of COVID-19 events which were scored by the adjudication committee as symptomatic-primary and symptomatic-non primary events combined considering only SD/SD treatment were provided upon request. When taking into account all events reported by the investigators before adjudication the point estimates of vaccine efficacy were about 5% lower.

Primary Efficacy Endpoint

At the time of the final analysis (DCO 7 December 2020), there was a total of 322 cases of virologically-confirmed COVID-19 occurring 15 or more days after the second dose, 82 in the AZD1222 group and 240 in the control group.

The table below shows the vaccine efficacy as determined in the predefined analysis (SD/SD+LD/SD seronegative for efficacy analysis set, any dosing interval) at the DCO 7 December 2020, as well as vaccine efficacy estimates of the intended dose and regimen as intended to be used in practice, i.e. based on the SD/SD population with an interval of minimally 4 weeks and the SD/SD population with an interval of 4 to 12 weeks between doses (as per section 4.2 in the SmPC). Further, as this is a pooled analysis, but the protocols and implementation of those protocols contain some differences, the effects for the two studies included in the pooling are also included to judge the consistency of effects estimated from the individual studies (DCO 4 November).

The high number of study participants who are included in the DCO 7 December vs. the previous DCO is due to the individuals who were post Dose1 and pre-Dose2 in November who then became post Dose2 in Dec at DCO2; the high number reflects a high recruitment rate in October.

Table 25: Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance (based on COV002, COV003, SD/SD Seronegative for efficacy analysis set)

	AZD1222	Control	Vaccine Efficacy (%)	95 CI (%)
SD/SD + LD/SD Seronegative for Efficacy Analysis Set (Primary)[a]	(N=7485) 82 (1.10)	(N=7475) 240 (3.21)	66.5	(56.91, 73.88)
SD/SD Seronegative for Efficacy Analysis Set [a]	(N=6106) 72 (1.18)	(N=6090) 189 (3.10)	62.6	(50.93, 71.46)
SD/SD Seronegative for Efficacy, 4-12 weeks interval [a]	(N=5258) 64 (1.22)	(N=5210) 154 (2.96)	59.5	(45.8, 69.7)
SD/SD Seronegative for Efficacy Analysis Set (UK, COV002) [b]	(N=2377) 15 (0.63)	(N=2430) 38 (1.56)	60.4	(28.0, 78.2)
SD/SD Seronegative for Efficacy Analysis Set (Brazil, COV003) [b]	(N=2063) 12 (0.58)	(N=2025) 33 (1.63)	64.2	(30.7, 81.5)
SD/SD Seronegative for Efficacy Analysis Set, 4-12 weeks interval (UK, COV002) [b]	(N=1669) 11 (0.66)	(N=1689) 26 (1.54)	57.9	(14.8, 79.1)
SD/SD Seronegative for Efficacy Analysis Set, 4-12 weeks interval (Brazil, COV003) [b]	(N=1970) 12 (0.61)	(N=1936) 32 (1.65)	63.3	(28.8, 81.1)
LDSD Seronegative for Efficacy Analysis Set [b, c]	(N=1367) 3 (0.22)	(N=1374) 30 (2.18)	90.1	(65.8, 97.1)

[a] Data from data cutoff date 07 December 2020
[b] Data from data cutoff date 04 November 2020
[c] Exploratory analysis, see further below
Source: First package Tables 1.3.1.1, 1.3.1.2 and Supplemental Table IEMT 207.1

In participants seronegative at baseline who received SD/SD or LD/SD and with follow up ≥ 15 days after the second dose, the vaccine efficacy of AZD1222 against COVID-19 was 66.5% (95% CI: 56.9%, 73.9%) ($p < 0.001$). 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 Cox Proportional Hazard model provided similar results to those observed for the primary analysis (as treated). A supportive analysis of the primary endpoint where patients were analysed according to the treatment to which they were randomized and regardless of the treatment actually received (ITT principle) provided similar results.

Due to the low dose dosing (LD/SD) in some participants and due to the relatively long window between the first and second dose (71% of LD/SD vaccinees received the second dose >12 weeks interval vs. 25% of SD/SD vaccinees), the VE estimate from the primary analysis (SD/SD + LD/SD Seronegative for Efficacy Analysis Set) does not convey the expected protective efficacy of AZD1222 as it may be in practice. As the

SD/SD is the intended regimen to be used in real life, the estimated VE based on the SD/SD seronegative at baseline population are expected to provide a better approximation of the expected efficacy.

In seronegative participants at baseline who received SD/SD, the vaccine efficacy of AZD1222 against COVID-19 ≥15 days after the second dose was 62.6% (95% CI: 50.9%, 71.5%). When restricting the analysis to subjects who received SD/SD with an interval of 4 to 12 weeks between doses, the vaccine efficacy ≥15 days after the second dose was similar at 59.5% (95% CI: 45.8, 69.7). Efficacy was consistent between studies COV002 and COV003.

The Kaplan Meier cumulative incidence plots for the SD/SD Seronegative for Efficacy, 4-12 week dose interval (data cut-off date 4th November), for the pooled analysis as well as individual studies COV002 and COV003 are provided below.

Figure 4: IEMT109 Cumulative incidence plot for time to first SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose of study intervention (SD/SD seronegative for efficacy, 4-12-week dose interval)

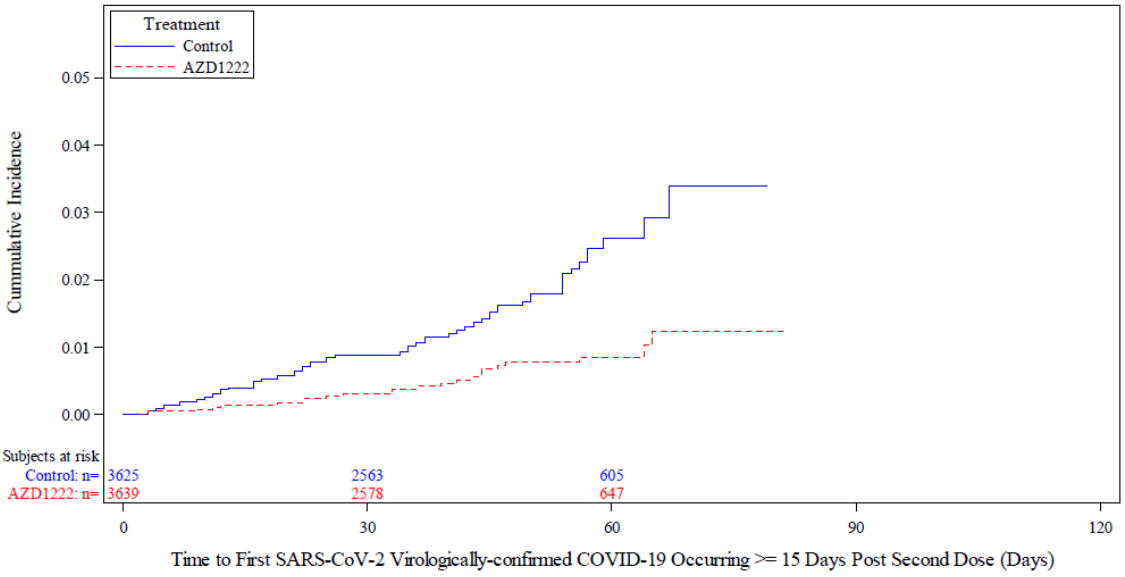
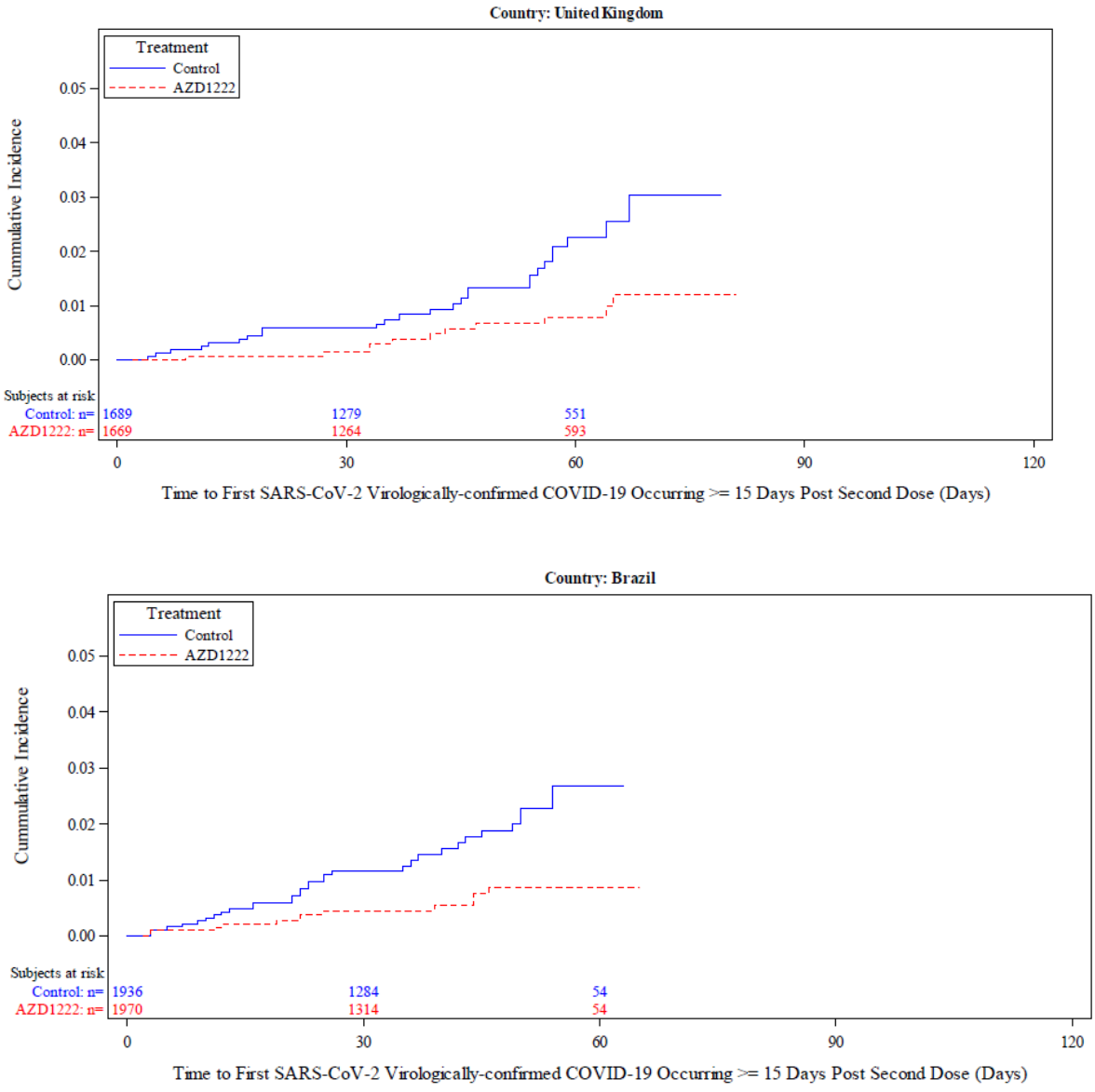


Figure 5: IEMT109 Cumulative incidence plot for time to first SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥15 days post second dose of study intervention by Country (SD/SD seronegative for efficacy, 4-12-week dose interval) UK and Brazil




```
Data cutoff date: 04NOV2020
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
amplificationtest.
```

To ensure robustness of the primary endpoint the applicant provided an overview per study and treatment arm of the number of calls received reporting COVID-related symptoms (for the 4 November data cut),

number of swabs taken and number of positive and negative tests. The proportion of negative swabs were similar between the treatment arms within the studies.

Secondary Efficacy Endpoints

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

Vaccine efficacy of AZD1222 against first SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥15 days after the second dose including severe and hospitalised cases are presented in Table 26 for the SD/SD Seronegative for Efficacy Analysis Set (dosing interval 4 to 12 weeks) (DCO 7 December 2020). The first line represents the overall Vaccine efficacy against virologically-confirmed COVID-19 of any severity, i.e. including cases with severity WHO grade ≥4.

Regarding efficacy against severe cases (WHO severity grade ≥6), for the 07 December 2020 data cut off in the SD/SD seronegative >15 days post-dose 2 set, there were 0 severe cases in the AZD1222 group and 1 case in the control group. In the same analysis set there were no cases that required ICU admission and there were no deaths due to COVID-19. In the Any Dose for Efficacy Analysis Set (DCO 4 November 2020), including all cases occurring any time after the first dose, there were 2 severe COVID-19 cases, one of which was fatal, in the control group. There were no severe cases in the AZD1222 group.

Regarding efficacy against hospitalisation (WHO Severity grade ≥4), in the DCO 7 December 2020 (SD/SD seronegative >15 days post-dose 2 set) there were 0 cases of COVID-19 hospital admission in the AZD1222 group (0.0%; N=5,258), compared to 8 in the control group (0.2%; N=5,210), including one severe case (WHO Severity grading ≥6) reported for control.

In the Any Dose for Efficacy Analysis Set, there were 16 cases of COVID-19 hospital admissions in the control group and 2 COVID-19 hospital admissions in the AZD1222 group. In the AZD1222 group, this included one case of score 4 and one case of score 5 on the WHO Clinical progression scale. For those who received the control, there were six cases of score 4, eight cases of score 5, one case of score 6 and one case of score 10.

In all participants who received at least one dose (any dose for efficacy analysis set, DCO 7 December 2020), as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received AZD1222, as compared to 14 (0.2%, N=8,026) reported for control, of which 2 severe (WHO scale ≥6), 1 requiring ICU (WHO scale ≥6) and 1 death (WHO scale 10).

Table 26: Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥15 Days Post Second Dose in the Pooled Analysis Set (COV002 + COV003), DCO2 (07 December 2020)

Analysis set Events	Participants with events AZD1222 n / N (%)	Participants with events Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD seronegative for efficacy analysis set, 4 to 12 weeks dosing interval					
COVID-19 [a]	64 / 5258 (1.22)	154 / 5210 (2.96)	59.50	(45.82, 69.72)	<0.001
Hospitalisation [b]	0 / 5258 (0)	8 / 5210 (0.15)	100	(42.65, NE)	0.007
Severe [c]	0 / 5258 (0)	1 / 5210 (0.02)	-	-	-
Requiring ICU [d]	0 / 5258 (0)	0 / 5210 (0)	-	-	-
Death [e]	0 / 5258 (0)	0 / 5210 (0)	-	-	-

[a] COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade ≥ 4.

[b] COVID-19 hospital admission is defined as WHO clinical progression scale ≥ 4.

[c] COVID-19 severe disease is defined as WHO clinical progression scale ≥ 6.

[d] COVID-19 ICU admission is defined as WHO clinical progression scale ≥ 7.

[e] COVID-19 death is defined as WHO clinical progression scale = 10.

Data cut-off: DCO2 (07 December 2020)

COVID19: 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.

Hospitalisation: 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 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.

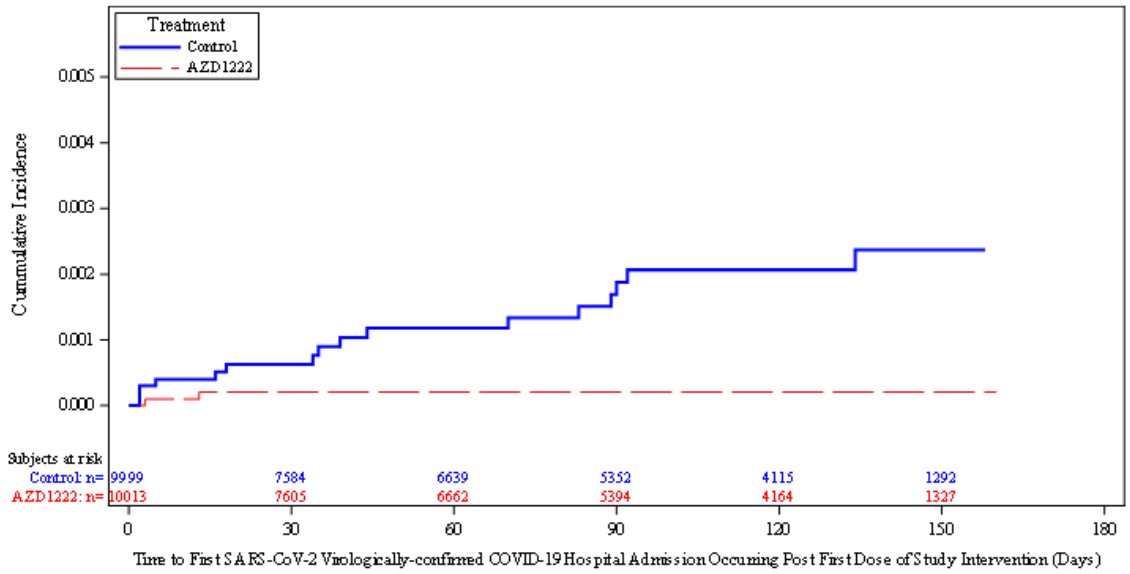
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.

The 4 to 12 weeks dosing interval range corresponds to ≥ 28 days to ≤ 84 days.

Abbreviations: CI = Confidence Interval; ICU = Intensive Care Unit; NE = Not Evaluable; VE = Vaccine Efficacy.

Source: Supplemental Tables IEMT 207.1, IEMT 207.2, IEMT 207.3, IEMT 207.4, IEMT 207.5.

Figure 6: Cumulative incidence plot for time to first SARS-CoV-2 virologically confirmed symptomatic COVID-19 hospital admission occurring post-first dose (any dose for efficacy analysis set, any serostatus)



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of first dose of study intervention + 1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.

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

COVID-19 endpoints are based on adjudicated events.

Source: Supplemental Figure IEMT35.

Efficacy against Asymptomatic SARS-CoV-2 Infection

Asymptomatic SARS-CoV-2 infection was assessed in study COV002 only. Vaccine Efficacy for incidence of first asymptomatic SARS-CoV-2 infection occurring ≥15 days after the second dose (SD/SD Seronegative for Efficacy Analysis Set, dosing interval 4 to 12 weeks) is summarised in the table below. Numbers are small and do not provide sufficient evidence to make conclusions regarding the efficacy of AZD1222 against asymptomatic SARS-CoV-2 infection.

Table 27: Vaccine efficacy for incidence of first asymptomatic SARS-CoV-2 infection occurring ≥15 days post second dose using Poisson regression with robust variance (COV002 only, DCO 07 December 2020)

Analysis set Event	Participants with events AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD seronegative for efficacy analysis set, 4 to 12 weeks dosing interval (COV002 only)					
Asymptomatic SARS-CoV-2 Infection	13 / 1956 (0.66)	14 / 1978 (0.71)	7.66	(-96.25, 56.55)	0.836

Asymptomatic infection was assessed in COV002 only.
Data cut-off: DCO2 (07 December 2020)
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.
Asymptomatic SARS-CoV-2 infections are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
The 4 to 12 weeks dosing interval range corresponds to ≥ 28 days to ≤ 84 days.
Abbreviations: CI = Confidence Interval; VE = Vaccine Efficacy.
Source: Supplemental Table IEMT 207.6.

Ancillary analyses

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

Using the COVID-19 primary case definition (SD/SD+LD/SD seronegative for efficacy set), VE was very similar for those with comorbidities at baseline [73.43 % (95% CI: 48.49, 86.29)] and those without comorbidities [68.2% (95% CI : 46.85, 81.05)] (DCO 04 November 2020).

At the DCO 7 December 2020, for the SD/SD efficacy set the estimates of VE was very similar for those with comorbidities at baseline [58.3% (95% CI: 33.6, 73.9)] and those without comorbidities [59.1% (95% CI: 40.50, 71.84)].

Efficacy Against COVID-19 in Older Adults (≥ 65 years of age, DCO 7 December 2020)

When using the primary case definition in the SD/SD Seronegative for Efficacy set ≥15 Days Post Second Dose, 4 case were detected in the vaccine group and 7 cases in the control group. This resulted in an estimate of VE of 44.8% (95% CI: -88.8, 83.88).

A low number of older adults ≥ 65 years of age (1353 total participants) were enrolled and included in the SD/SD Seronegative for Efficacy Analysis Set (N = 687 for AZD1222 and N = 666 for control). Older adults were enrolled late in the trials following a safety risk-adverse age escalation strategy. Therefore there was limited follow up time available for this group of older adults in the pooled efficacy analysis. The median duration of follow up after the first dose was 71.0 days and 15 days after the second dose was 20.0 days. A large proportion (85%) of older adults received their second dose <6 weeks after their first dose.

Efficacy Against COVID-19 in Adults 56-65 years of age (DCO 7 December 2020)

Vaccine efficacy was analysed according to the primary case definition also for subjects 56-65 YOA for the SD/SD seronegative efficacy population. This subgroup analysis was prespecified because COV002 and

COV003 studies were randomised by 18-55, 56-70, 70+ YOA. Due to few cases in this age subgroup, an efficacy estimate could not be determined. In the overall pooled efficacy set there were 8 cases in the AZD1222 group and 9 cases in the control group in subjects 56-65 years of age.

Efficacy in seropositive subjects

There were few subjects seropositive at baseline (373 subjects in total, DCO 4 November 2020). The number of seropositive participants in Any Dose Efficacy was too small for a meaningful analysis of the incidence of COVID-19 (0/185 cases in the AZD1222 group and 1/188 cases in the control group). No reliable estimates of VE by serostatus at baseline can be presented.

Efficacy by dose interval

Vaccine efficacy for incidence of first SARS-CoV-2 virologically-confirmed symptomatic COVID-19 occurring ≥ 15 Days after the second dose in the SD/SD Seronegative for Efficacy Analysis Set (for COV002, COV003, and overall) has been summarised by dosing interval (4–8 Weeks, 9–12 Weeks, and > 12 Weeks) in Table 28 below.

Table 28: Vaccine Efficacy for Incidence of First SARSCoV2 Virologically Confirmed Symptomatic COVID19 Occurring ≥15 Days Post Second Dose by Dose Interval (SDSD Seronegative for Efficacy Analysis Set): 4–8 Weeks, 9–12 Weeks, > 12 Weeks, and 4-12 Weeks (DCO2: 07 December 2020)

Study Dose interval	Participants with events, n (%) AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
COV002 (UK)					
4–8 weeks	11 /1228 (0.90)	20 / 1180 (1.69)	49.37	-5.49, 75.70	0.069
9–12 weeks	6 / 728 (0.82)	29 / 798 (3.63)	77.50	45.82, 90.66	<0.001
> 12 weeks	6 / 708 (0.85)	27 / 744 (3.63)	77.02	44.28, 90.52	0.001
4-12 weeks	17 / 1956 (0.87)	49 / 1978 (2.48)	65.49	40.14, 80.11	<0.001
Any interval	23 / 2692 (0.85)	77 / 2751 (2.80)	70.02	52.56, 81.18	<0.001
COV003 (Brazil)					
4–8 weeks	42 / 2981 (1.41)	95 / 2934 (3.24)	56.96	38.13, 70.05	<0.001
9–12 weeks	5 / 321 (1.56)	10 / 298 (3.36)	54.33	-33.12, 84.33	0.151

> 12 weeks	2 / 99 (2.02)	6 / 84 (7.14)	72.80	-33.86, 94.47	0.109
4-12 weeks	47 / 3302 (1.42)	105 / 3232 (3.25)	56.75	39.03, 69.32	<0.001
Any interval	49 /3414 (1.44)	112 / 3339 (3.35)	57.61	40.73, 69.68	<0.001
Pooled (COV002 + COV003)					
4–8 weeks	46 / 3728 (1.23)	88 / 3639 (2.42)	50.40	29.19, 65.25	<0.001
8–12 weeks	18 / 1530 (1.18)	66 / 1571 (4.20)	72.10	53.03, 83.42	<0.001
> 12 weeks*	8 / 807 (0.99)	33 / 828 (3.99)	75.40	46.70, 88.65	<0.001
4-12 weeks*	65 / 5832 (1.11)	156 / 5763 (2.71)	59.41	45.82, 69.59	<0.001
Any interval*	74 / 6845 (1.08)	192 / 6794 (2.83)	62.17	50.56, 71.05	<0.001

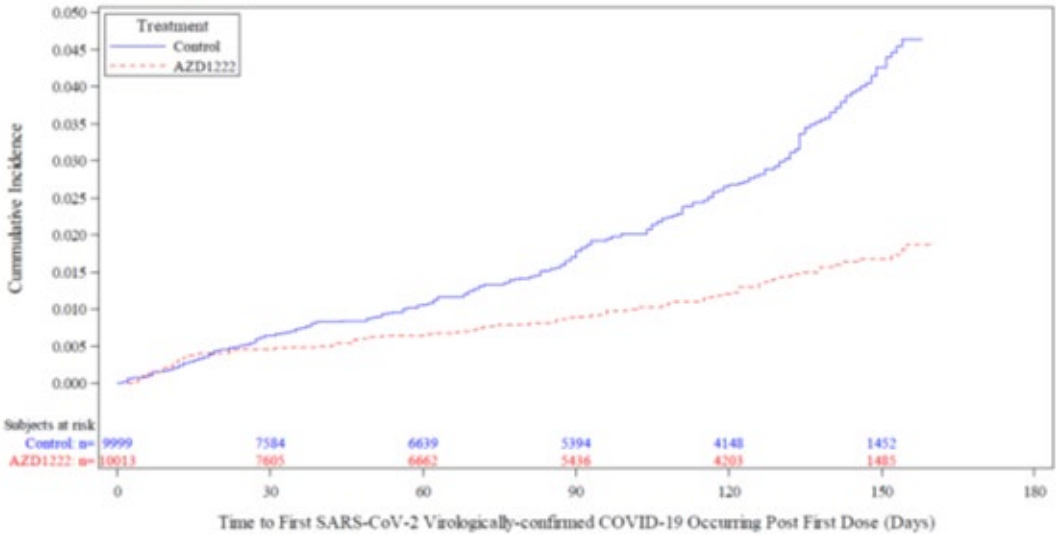
*DCO 4 November 2020

Efficacy post dose 1 and before dose 2 (DCO 4 November 2020)

Based on data cut off 4 November 2020, efficacy of the AZD1222 vaccine was estimated at 50.5% (95% CI: 36.5, 61.5) against COVID-19 in participants who received at least one dose with follow up from the first dose (Any dose for Efficacy Analysis set, seronegative at baseline). The efficacy between dose 1 and dose 2 was estimated to be 42.8% (95% CI: 20.3, 59.0) (see Table 30).

The Cumulative Incidence curves in Figure 7 showed divergence from approximately 21 days after the first dose, indicating induction of protective immunity by 21 days after the first dose.

Figure 7: Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus) (DCO 4 November 2020)



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

Therefore, an ad hoc analysis was conducted to determine whether protective immunity was induced by the first dose (Table 29). The analysis was based on a follow-up time from 22 days after the first dose and was censored at the time of the second dose; participants who had not received a second dose were censored at the time of the data cut-off, discontinuation, or COVID-19 event. For those participants who had SD as their first dose, vaccine efficacy was estimated between 22 days after dose 1 through the second dose (71.30% 95% CI: 49.02, 83.84).

Table 29: Vaccine Efficacy for Incidence of First SARS CoV2 Virologically confirmed Symptomatic COVID 19 Occurring ≥22 days after dose 1 up to dose 2 (DCO 4 November 2020)

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

[a] Includes participants who were seronegative at baseline.

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

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

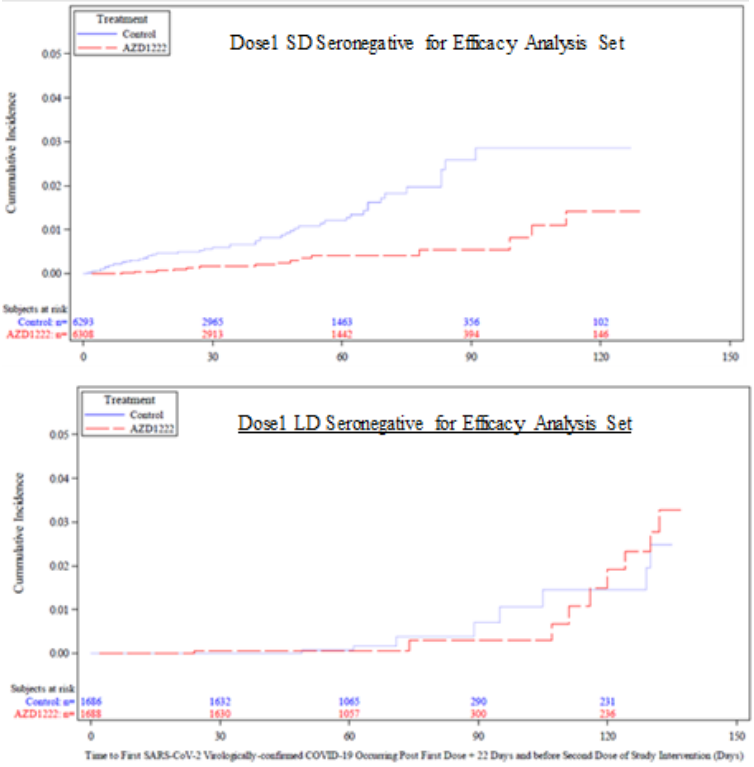
The follow up time beginning 22 days post 1st dose and before 2nd dose, or event, or discontinuation, or data cut-off, whichever is earliest. Participants who only received their first dose are also included in the analysis until event, discontinuation or data cut-off, whichever is earlier.

Source: Supplemental Tables IEMT57.1.2 and IEMT57.1.3.

Cumulative Incidence plots show divergence up to 12 weeks post first dose, but the amount of data is very limited past this point (Figure 8 below).

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

Figure 8: Cumulative Incidence Plots for Time to First Sars-CoV-2 Virologically Confirmed COVID-19 Occurring Post First Dose +22 Days and Before Second Dose of Study Intervention (DCO 4 November 2020)



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose + 22 days before second dose of study intervention, in days, has been calculated as follows: Date of first SARS-CoV-2 virologically confirmed test occurring 22 days post first dose before second dose –(date of first dose of study intervention +22) +1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.
COVID-19 endpoints were based on adjudicated events.
Source: Supplemental Figures IEMT59.1 and IEMT59.2.

In a further exploratory analysis of the 4 November dataset into the vaccine efficacy 22 days post dose 1 censored at either 12 weeks post dose 1 or at dose 2, whichever came first, the estimated VE for the pooled dataset was 73.0% (95%CI: 48.9, 85.8). The same analysis gave an estimate of 44.1% (-66.8, 81.3) in COV002, with wide confidence intervals and 80.2% (55.3, 91.2) in COV003. This table also lists the efficacy analyses that were initially done after dose 1 and between dose 1 and 2, which were mentioned at the beginning of the paragraph.

Table 30: Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 by Country and Time Post Dose 1 or Between Dose 1 and Dose 2 (Any Dose for Efficacy Analysis Set – Seronegative at Baseline and Dose 1 SD) (DCO 4 November 2020)

Study Time Period	Participants with events, n (%)		VE (%)	95% [a] or 97.5% [b] CI (%)
	AZD1222 n / N (%)	Control n / N (%)		
COV002 (UK)				
Post Dose 1	31 / 3217 (0.96)	64 / 3216 (1.99)	51.6	25.9, 68.5
Post Dose 1 – before Dose 2	11 / 3217 (0.34)	18 / 3216 (0.56)	39.4	-28.3, 71.3
Dose 1 + 21 days – Dose 2 [c]	5 / 3067 (0.16)	9 / 3068 (0.29)	44.1	-66.8, 81.3
COV003 (Brazil)				
Post Dose 1	61 / 4791 (1.27)	121 / 4797 (2.52)	50.0	31.9, 63.2
Post Dose 1 – before Dose 2	44 / 4791 (0.92)	78 / 4797 (1.63)	43.6	18.3, 61.0
Dose 1 + 21 days – Dose 2 [c]	7 / 3343 (0.21)	35 / 3324 (1.05)	80.2	55.3, 91.2
Pooled (COV002 + COV003)				
Post Dose 1	92 / 8008 (1.15)	185 / 8013 (2.31)	50.5	36.5, 61.5
Post Dose 1 – before Dose 2	55 / 8008 (0.69)	96 / 8013 (1.20)	42.8	20.3, 59.0
Dose 1 + 21 days – Dose 2 [c]	12 / 6410 (0.19)	44 / 6392 (0.69)	73.0	48.9, 85.8

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

b) The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided CI 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 infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio was derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

c) Censored at 12 weeks post Dose 1.

Data cut-off date: 04 NOV 2020.

Abbreviations: CI = Confidence Interval. VE = Vaccine Efficacy.

Source: Supplemental Table IEMT 119.10-27. Supplemental Tables IEMT 37.1.2, and IEMT 119.1–9.

The table below describes vaccine efficacy from 22 days after dose 1 up to different time periods post-dose 1, per country and pooled.

Overall the data show that there is a protective effect by Day 22 post Dose 1 of AZD1222 that persists up to Dose 2 or 12 weeks after Dose 1.

Table 31: Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Using Poisson Regression with Robust Variance by Country and Time Post Dose 1 (Dose 1 Seronegative for Efficacy Analysis Set) (DCO 4 November 2020)

Study Time Period	Participants with events, n (%)		VE (%)	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
COV002 (UK)					
≥ 22 days post Dose 1 – Week 4	0 / 3060 (0)	1 / 3064 (0.03)	100	-3805.10, NE	>0.999
≥ 22 days post Dose 1 – Week 6	1 / 3060 (0.03)	3 / 3064 (0.10)	66.70	-220.16, 96.54	0.341
≥ 22 days post Dose 1 – Week 8	1 / 3060 (0.03)	4 / 3064 (0.13)	74.91	-124.52, 97.20	0.216
≥ 22 days post Dose 1 – Week 10	4 / 3060 (0.13)	6 / 3064 (0.20)	32.80	-138.03, 81.03	0.538
≥ 22 days post Dose 1 – Week 12	4 / 3060 (0.13)	9 / 3064 (0.29)	55.25	-45.24, 86.21	0.181
≥ 22 days post Dose 1 – Week 14	5 / 3060 (0.16)	12 / 3064 (0.39)	58.14	-18.74, 85.24	0.102
≥ 22 days post Dose 1 – Dose 2	8 / 3060 (0.26)	16 / 3064 (0.52)	50.53	-15.43, 78.80	0.104
COV003 (Brazil)					
≥ 22 days post Dose 1 – Week 4	0 / 3247 (0)	10 / 3232 (0.31)	100	55.59, NE	0.002
≥ 22 days post Dose 1 – Week 6	2 / 3247 (0.06)	20 / 3232 (0.62)	90.13	57.77, 97.69	0.002
≥ 22 days post Dose 1 – Week 8	4 / 3247 (0.12)	25 / 3232 (0.77)	84.14	54.46, 94.48	<0.001
≥ 22 days post Dose 1 – Week 10	5 / 3247 (0.15)	30 / 3232 (0.93)	83.47	57.43, 93.58	<0.001
≥ 22 days post Dose 1 – Week 12	6 / 3247 (0.18)	33 / 3232 (1.02)	81.94	56.94, 92.43	<0.001
≥ 22 days post Dose 1 – Week 14	6 / 3247 (0.18)	36 / 3232 (1.11)	83.39	60.62, 92.99	<0.001
≥ 22 days post Dose 1 – Dose 2	6 / 3247 (0.18)	36 / 3232 (1.11)	83.31	60.44, 92.96	<0.001
Pooled (COV002 + COV003)					
≥ 22 days post Dose 1 – Week 4	0 / 6307 (0)	11 / 6296 (0.17)	100	60.55, NE	<0.001

Table 31: Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Using Poisson Regression with Robust Variance by Country and Time Post Dose 1 (Dose 1 Seronegative for Efficacy Analysis Set) (DCO 4 November 2020)

Study Time Period	Participants with events, n (%)		VE (%)	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
≥ 22 days post Dose 1 – Week 6	3 / 6307 (0.05)	23 / 6296 (0.37)	87.25	57.32, 96.19	<0.001
≥ 22 days post Dose 1 – Week 8	5 / 6307 (0.08)	29 / 6296 (0.46)	83.07	56.13, 93.47	<0.001
≥ 22 days post Dose 1 – Week 10	9 / 6307 (0.14)	36 / 6296 (0.57)	75.26	48.50, 88.12	<0.001
≥ 22 days post Dose 1 – Week 12	10 / 6307 (0.16)	42 / 6296 (0.67)	76.38	52.86, 88.17	<0.001
≥ 22 days post Dose 1 – Week 14	11 / 6307 (0.17)	48 / 6296 (0.76)	77.19	56.03, 88.16	<0.001
≥ 22 days post Dose 1 – Dose 2	14 / 6307 (0.22)	52 / 6296 (0.83)	73.21	51.67, 85.15	<0.001

Data cut-off 04 November 2020.
Abbreviations: CI = Confidence Interval; NE = not evaluable; VE = Vaccine Efficacy.
Pooled analysis: 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 (for the pooled analysis). UK and Brazil: 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. Country analysis: 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.
COVID-19 events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
The participants are censored before the second dose of Study Intervention or the stated number of weeks post the first dose if earlier.
Source: Supplemental Table IEMT156.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of Efficacy for the pooled analysis from trials COV002 and COV003 (SD/SD efficacy set, interval between doses 4-12 weeks)

Title: Pooled efficacy analysis (data pooling from study COV002 and COV003) **COV002**: Phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 **COV003**: A Randomized, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine.		
Study identifier	COV002: EudraCT number: 2020-001228-32 REC Reference: 20/SC/0179 IRAS Reference: 281904 COV003: Study code COV003 Registration number: ISRCTN89951424	
Design	Both studies were single-blind, randomised, multicentre safety and efficacy study, with immunogenicity sub studies in older and younger age groups	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Follow-up of 12 months after the first dose not applicable not applicable
Hypothesis	Superiority versus non-COVID vaccine/saline	
Treatments groups	AZD1222 vaccine	**Dose of AZD1222 per administration:** the nominal dose should have been 5 x 10^{10} VP for all study participants (see AR) 2.2 x 10^{10} vp (qPCR) 2.5 x 10^{10} vp (qPCR) 5 x 10^{10} VP (Abs 260) 5 x 10^{10} VP (qPCR) 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* *The amount of adenovirus was determined by qPCR, absorbance at 260nm (Abs 260), or Abs 260, corrected for the absorption on the component PS80 2 doses of ChAdOx1 nCoV-19 (AZD1222) vaccine, with a variable interval between doses of between 3 and 26 weeks 10014 randomized for any dose for efficacy

	Control		**Dose of Control per administration**: Meningitis (MenACWY) vaccine or saline (for second dose) 2 IM injections (either MenACWY or saline) 10000 randomized for any dose for efficacy
Endpoints and definitions	**Primary endpoint** Overall and by subgroups: Country Comorbidities Age Dose interval		Incidence of SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention Only the SD/SD Seronegative population with a dose interval of 4-12 weeks has been considered
	Secondary Severe COVID-19 disease		Severity as in WHO classification
	Secondary Hospital Admissions		
Database lock	7 December 2020		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis (data are derived from post—hoc analysis)**	
Analysis population and time point description	SD/SD Seronegative population After ≥15 days post-second dose Time interval between doses 4-12 weeks	
Primary endpoint Overall	**AZD1222 vaccine** n=6106 **Control** n=6090	Cases AZD1222 64/5258 Cases Control 154/5210
	Vaccine Efficacy %	**59.50**
	95% CI	45.82, 69.72

Primary endpoint Subgroup 18-64 years	Cases AZD1222 60/4572 Cases Control 147/4545	
	Vaccine Efficacy %	**59.98**
	95% CI	45.98, 70.35
Primary endpoint Subgroup ≥65 years	Cases AZD1222 4/686 Cases Control 7/665	
	Vaccine Efficacy %	**44.83**
	95% CI	-88.77, 83.88
Analysis description	**Secondary analysis**	
Secondary endpoint Severe disease	Cases AZD1222 0/6845 Cases Control 1/6794	
	Vaccine Efficacy %	100
	97.5% One-sided CI	(-3742.53, NE)
Secondary endpoint Hospital Admissions	Cases AZD1222 0/6845 Cases Control 8/6794	
	Vaccine Efficacy %	100
	97.5% One-sided CI	(42.58, NE)

2.5.3. Discussion on clinical efficacy

This application is based on data from the first 4 studies of this clinical program: COV001 (Phase I/II- UK); COV002 (Phase II/III-UK); COV003 (Phase II/III-Brazil) and COV005 (Phase I/II-South Africa), which were all sponsored by the University of Oxford. Substantial additional clinical data is only expected from study

D8110C00001, an ongoing phase 3 confirmatory trial in approximately 30,000 subjects which is being conducted in US, Chile and Peru. The results of this trial will need to be submitted to further supplement data in important subgroups including older adults and subjects with underlying disease, and to further consolidate the results from the pooled analysis.

GCP aspects

Studies were initiated by an academic sponsor. The applicant was involved in the development at a later stage. The dossier suffers from a lack of sponsor oversight which impacts the reporting of data and therefore data integrity. This was identified by GCP inspections of COV001 and COV002, and although CAPAs were initiated it is not entirely clear how well these were implemented and how successful these have been. Indeed, minor inconsistencies of the data are still observed in some areas, and questions have been raised to address these issues. Nonetheless, after careful review of all data submitted and of the DSMB minutes, the CHMP is convinced that, despite the unconventional approach taken in the studies and the remaining uncertainties, the data are sufficiently robust to allow conclusions regarding efficacy and safety of AZD1222.

Design and conduct of clinical studies

Individual studies

Study COV001 is a First in Human Phase I/II, single-blinded, controlled, individually randomised study that enrolled 1077 healthy volunteers aged 18-55 years in the UK.

Study COV002 is a Phase II/III, participant-blinded individually randomized controlled trial in adults and healthy children in the UK. In total, the study included 12,390 participants that were distributed in 12 study groups (Groups 1-12), including different age groups which received doses from different manufacturing processes. Of these 12 groups, only groups 4 and 6 (adults aged 18 - 55 years), 9 (adults aged 56-69 years), and 10 (adults aged 70 years and older) were included in the pooled efficacy analysis. This makes sense since the other groups, which were small (up to 60 subjects each), recruited very specific populations such as HIV patients or subjects that previously received a ChAdOx1 vectored vaccine. Due to miscalculation of the potency of one vaccine batch, in total 1716 participants in Group 4 received a LD vaccine (2.2×10^{10} vp) as the first injection then followed by a second SD vaccine injection (5×10^{10} vp). COV002 also includes weekly self-swabs for detection of asymptomatic infection.

The impact of pre-existing anti-vector immunity is expected to be minimal in the context of a 2-dose vaccine regimen (see section 2.4).

Study COV003 is a phase III, controlled, randomized, single-blind study which is ongoing in adults 18 years of age and older with high exposure to COVID-19 (mainly health-care workers). In total 10,002 participants were recruited in Brazil.

Study COV005 is an ongoing adaptive phase I/II randomized, double-blinded, placebo-controlled trial to determine safety, immunogenicity and efficacy of AZD1222 vaccine in South African adults aged 18-65 years without HIV, and safety and immunogenicity in adults with HIV. For this study, 2,096 participants were recruited.

The four studies (COV001, COV002, COV003 and COV005) have several aspects in common that made them suitable for pooling. All studies enrolled adults 18 to 55 years of age, and in addition, studies COV002 and COV003 have enrolled older adults from 56 years of age. Inclusion and exclusion criteria were generally

similar across studies. Enrolment in the initial Phase I Study COV001 was restricted to healthy adults, which is considered adequate for a FIH study especially considering the potential risk of Vaccine Associated Enhancement of Disease (VAED). The other studies allowed the inclusion of participants with underlying health conditions with the exception of severe and/or uncontrolled underlying disease. All studies excluded pregnant and breastfeeding women. Subjects with a confirmed or suspected immunosuppressive or immunodeficiency state were also excluded, as were subjects with a history of serious allergies. Subjects with a known history of laboratory confirmed COVID-19 were also excluded. Several of the trials enrolled individuals working in professions with higher risk of exposure to SARS-CoV-2, such as health and social care settings.

Participants received AZD1222 or control (licensed MenACWY vaccine in trials COV001, COV002 and COV003, or saline in trials COV003 and COV005). In trials in which a licensed MenACWY vaccine was administered, the trial staff administering the vaccines were not blinded to the vaccine to be administered (single-blinded trials). This aspect is not considered to have influenced the results obtained from these trials. In the FIH trial (COV001), subjects seropositive to SARS-CoV-2 at baseline were excluded, but this criterion was removed in other trials, hence immunogenicity and safety data from subjects seropositive at baseline were obtained.

As detailed in the Pharmacology section, the initial intent of this programme was to implement a one dose of 5×10^{10} vp immunization schedule, but following review of immunogenicity data from COV001 indicating that a second dose provided increased immunogenicity, the protocols for the four trials were amended to incorporate a second dose. This relatively late decision, together with delays in material availability for second dose vaccinations, resulted in the interval between doses 1 and 2 to range from 4 to 26 weeks instead of the originally intended 4 to 12 weeks interval.

Studies COV001 and COV005 were originally planned to contribute to pooled interim analysis for efficacy. However, COV001 did not meet the predetermined criterion of at least 5 cases of COVID-19 and COV005 was not pooled as the primary endpoint definition differed.

The evidence of efficacy for AZD1222 is therefore based on pooled data from studies COV002 and COV003.

Methods of the pooled efficacy analysis

The primary population for efficacy analysis was "SD/SD + LD/SD Seronegative for Efficacy" as prespecified in the SAP. It was also foreseen to analyse the SD/SD cohort as supportive of the primary analysis. The analysis of the LD/SD was post-hoc defined as an exploratory subgroup analysis. The subgroups proposed for assessing the efficacy, safety, and immunogenicity among different populations are considered adequate.

Efficacy assessment

Overall, the primary and secondary efficacy endpoints are endorsed. The primary efficacy endpoint was calculated according to the "Incidence of SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention" but also as supportive information according to "Time to First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention" which is considered adequate. The same strategy was followed for the efficacy secondary endpoints. This approach is endorsed.

The case definition for primary efficacy analysis included symptomatic COVID-19 of any severity that has to be PCR-confirmed. The symptoms included in the case definition are in line with those reported by international institutions such as WHO, ECDC and CDC. Therefore, this case definition is supported.

It was considered adequate that a central, blinded, adjudication committee was used for all 4 studies to assess COVID-19 cases with SARS-CoV-2 virologically confirmed results. Each case was assessed by the blinded adjudication committee and classified according to the WHO severity grading scale.

The case definitions for secondary endpoints are also acceptable. It is considered adequate to have followed the WHO scale for disease progression. Nonetheless, the endpoint chosen by the Applicant "COVID-19: hospital admission" includes WHO cases with a score of four that include "hospitalized patients without oxygen therapy", i.e. does not have an objective clinical measures of the severity of respiratory disease for cases with a score of four according to WHO scale, which is a limitation. The case definitions for severe disease or ICU admission are considered adequate.

In relation to the PCR methodology used to confirm COVID-19 cases, 19 different methods were used in the UK studies (COV001 and COV002), 8 different methods for the Brazil study and one method for the South Africa study. Moreover, several laboratories in UK and Brazil performed the PCR testing. This situation is far from ideal, i.e. using a single validated PCR test (with high specificity and sensitivity) and all samples being tested in one Central Lab. However, based on assessment of the sensitivity, specificity, and validation status of all the PCR methods used in clinical studies it was concluded that the integrity of the study results was not compromised.

Statistical analysis plan (SAP)

The use of a Poisson regression model (including treatment, study code and age group) with robust variance as the primary efficacy analysis model to estimate the relative risk (RR) of the incidence of SARS-CoV-2 virologically-confirmed primary symptomatic COVID-19 between the AZD1222 and control groups is endorsed. It is also considered adequate to have supported the primary analysis with a Cox Proportional Hazards model using the same covariates as for the primary analyses as well as presenting Kaplan-Meier curves.

The secondary efficacy analysis was to be conducted in a similar manner as described above for the primary efficacy endpoint, which is adequate.

Conduct of the studies

Several changes have been made to the study protocols while the studies were conducted. For COV001 there were 12 revisions of the protocol, for COV002 14 revisions, for COV003 8 revisions and for COV005 4 revisions. It is acknowledged that conducting a rigorous vaccine trial during a pandemic under time pressure and with many uncertainties about the disease and the future course of the pandemic is a huge challenge. However, due to all the changes the trials should be viewed as a trial with an (unintentional) adaptive design. Adaptations in confirmatory trials introduced without proper planning reduce the confirmatory nature of the trial, and results of these (unintentional) adaptations should be considered exploratory.

In total, 30,198 subjects were screened (DCO 4 November 2020). Of these, 23,856 subjects were enrolled, and 23,745 were randomised (excluding 8 subjects randomised and not vaccinated). Differences in proportion of screening failures were observed between studies and individual sites. This may be related to differences in interpretation of inclusion and exclusion criteria. Overall, these differences are not likely to have had an impact on the overall trial results.

An overview of protocol deviations per study and site was evaluated. In COV003, significant differences were noted between sites in the number and type of protocol deviations, which are related to the follow up time at

different sites. Enrolment at three sites started 4 months later than the first three initial sites, hence the initial sites show more deviations.

Efficacy data and additional analyses

Participant Disposition

The pooled efficacy data is mostly based on the final data cut of 7 December 2020 (DCO2). For some analyses, these data were not yet available at the time of assessment, in which case the interim data from 4 November 2020 is shown.

The population sizes (AZD1222 plus control) of the "SD/SD+LD/SD", SD/SD and LD/SD sets were 11,636, 8,895 and 2,741 subjects, respectively. The disposition of subjects for the AZD1222 and the control group was similar in the different sets analysed. When considering the "any dose efficacy" set, only 100 out of 20,014 participants discontinued, which does not raise any concern in relation to trial integrity.

Studies COV002 and COV003 are still ongoing. As of the data cut-off date of 04 November 2020, 12,021 participants of the 4 studies included in the application had received at least one dose of AZD1222. Of these participants, 8,266 (68.8%) had received 2 doses of AZD1222. The "any dose for efficacy" set included a total of 1,161 subjects (576 and 585 in the vaccine and placebo group, respectively) who were seropositive to COVID-19 at baseline. It is also noted that 75 subjects had a PCR-confirmed COVID-19 prior to 15 days post second dose and were thus excluded from the "SD/SD+LD/SD" set.

Within each of the three sets (SD/SD, LD/SD and SD/SD+LD/SD) the disposition of subjects was well balanced according to the different baseline parameters. The population enrolled in the clinical studies mainly consisted of healthy adults 18 to 55 years of age. In the primary efficacy analysis population (SD/SD + LD/SD, seronegative), only 6% of participants were ≥ 65 years of age. Also, a small number of subjects (6.5%) from 56 to 65 YOA are included in this efficacy set and races other than "white" are poorly represented. The mean age was approximately 42 years old, 61% were female, 83% of participants were White and 36% of participants had a comorbidity at baseline.

When analysing the baseline data of the SD/SD and LD/SD groups separately, some baseline characteristics differ between the two groups. Specifically, the LD/SD group only includes subjects 18-55 YOA, by contrast the SD/SD group includes a higher proportion of elderly participants than the combined SD/SD+LD/SD (7.7% versus 5.7%). Regarding sex, the female proportion in the SD/SD group is 59.4% and 64.8% in the LD/SD group. The proportion of white subjects is lower in the SD/SD group than in the LD/SD (79.9% versus 92.2%).

Based on Demographics and Baseline Characteristics for the SDSD Seronegative for Efficacy Analysis Set, 4 to 12 Weeks Dosing Interval, at the DCO2 (07 December 2020), 12.9% of participants were ≥ 65 years of age and 2.8% >75YOA. Also, a small number of subjects (16.0%) from 56 to 69 YOA are included in this efficacy set and races other than "white" are poorly represented. The mean age was approximately 44 years old, 55.3% were female, 46.6% of participants were White and 39.2 % of participants had a comorbidity at baseline.

The most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%). Therefore, not all population groups that will likely be targeted for COVID-19 vaccination may be adequately represented in the studies. Regarding the interval between doses, important variability has been observed, as mentioned. In fact, 29.3% received the second dose within less than 6 weeks from the first dose, 9.8%

between 6 and 8 weeks, 24.9% between 9 and 11 weeks and 36.0% after more than 12 weeks. Moreover, it should be noted that the proposed dosing schedule in the SmPC is two doses administered with an interval of 4 to 12 weeks. Therefore, 36.0% of subjects were vaccinated outside of the 4-12 weeks dose interval.

Importantly, none of the subjects in the LD/SD group received the second dose less than 6 weeks from the first one. In fact, 71.6% of the subjects in this set received the second dose ≥12 weeks post first dose. The situation is very different for the SD/SD population, in which 38.2% of the subjects received the second dose less than 6 weeks from the first one, and 25.2% received the second dose ≥12 weeks post first dose. Dose interval confounded the analysis of VE according to dose level and increased dose interval has at least partially driven the observed high VE in the LDSD regimen

Duration of follow up was relatively short. At the DCO 07 December 2020, participants who received the second dose in the 4-12 weeks interval had a median duration of follow up of 78 days since the second dose (min 17, max 127), and a median duration of follow up from the first dose of 118.0 days (min 45, max 182).

Primary Efficacy Endpoint and Analysis

The efficacy of the AZD1222 vaccine ≥ 15 days post second dose was 66.5% (95% CI: 56.9, 73.9) against COVID-19 in seronegative participants at baseline who received SD/SD or LD/SD. The primary objective was met since the lower bound of the 95% CI of vaccine efficacy was above 20%.

The study was not designed to evaluate the effect of the dose level (i.e. LD/SD vs SD/SD) or the interval between the first and second dose.

Evaluation of the dose regimen LD/SD vs. SD/SD was included as an explorative subgroup analysis. The protective efficacy of the SD/SD regimen ≥15 days post second dose in subjects seronegative at baseline was 62% (95% CI: 40-76%) compared to 90% (95% CI: 66–97%) for the LD/SD regimen.

The vaccine efficacy calculated for the LD/SD group is much higher than that for the SD/SD group. It is not clear whether this effect can be attributed to the differences in dosing, an artefact due to distribution of risk factors between the SD/SD and LD/SD populations, due to different dose interval, or due to chance.

As the cause for this difference is not clear it is considered that this difference in vaccine efficacy casts doubts on the appropriateness of a pooled analysis across these two populations for the purpose of calculating the primary vaccine efficacy endpoint.

Thus, it is considered that vaccine efficacy estimated for the SD/SD set represents more faithfully the vaccine efficacy conferred by the vaccine as intended to be given in practice. In this regard the vaccine efficacy was 62.6% with a 95% CI (50.9, 71.5), thus the lower limit of the confidence interval is still higher than 20%. VE was similar for the SD/SD population both in the UK and Brazil trials.

Further, data are suggestive that vaccine efficacy was lower in subjects who received the second dose between 4- 8 weeks after the first dose as compared to those who received the second dose more than 8 weeks after the first dose. Taking into account the above mentioned observations and the fact that the CI of the different vaccine estimates for the different dose intervals are very wide it cannot be concluded on whether vaccine efficacy increases within the time interval between doses of 4-12 weeks, despite a trend in this direction is observed and would be compatible with current knowledge of priming and boosting of vaccines.

In conclusion, the efficacy will be based on the regimen as close as possible to the intent-to-treat principle: i.e. the efficacy measured in subjects who received the SD/SD regimen, with the second dose given at least four weeks after the first dose up to preferably 12 weeks after the first dose.

Secondary and Exploratory Efficacy Analysis

For the 7 December 2020 data cut off, there were 0 severe cases in the AZD1222 group and in those that received the control vaccine there was 1 case. In this same analysis set there were no cases that required ICU admission and there were no deaths due to COVID-19. In the Any Dose for Efficacy Analysis Set, including all cases occurring any time after the first dose, there were 2 severe COVID-19 cases, one of which was fatal, in the control group. There were no severe cases in the AZD1222 group.

There were 0 cases of COVID-19 hospital admission in the SD/SD since ≥ 15 days after the second dose in the AZD1222 group compared to 8 in the control group. In the Any Dose for Efficacy Analysis Set, there were 16 cases of COVID-19 hospital admissions in the control group and 2 COVID-19 hospital admissions in the AZD1222 group. In the AZD1222 group, this included one case of score 4 and one case of score 5 on the WHO Clinical progression scale that occurred shortly after first dose administration. For those who received the control, there were six cases of score 4, eight cases of score 5, one case of score 6 and one case of score 10. Indeed, two of these hospitalized cases for the vaccine group (and 2 for the control group) occurred before 22 days post first dose, when vaccine immunity may not be fully developed. So as from 22 days post dose 1 in all participants who received at least one dose, there were 0 (0.0%, N=8,032) cases of COVID 19 hospitalisation in participants who received the vaccine, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control. These data would support a beneficial effect of AZD1222 on preventing hospitalisations due to COVID-19.

No efficacy estimate of AZD1222 could be obtained against asymptomatic SARS-CoV-2 infection in the SD/SD set Seronegative for Efficacy for COV002 only, 4-12 w Dose Interval (i.e. 28 to 84 Day) [VE 7.66, 95% CI (-96.25, 56.55)]). There was a relatively low number of asymptomatic cases, which may have been a result of the once weekly swabbing, thus cases may have been missed. As the observed number of cases was low, effect estimates are imprecise. Further, although the presence of viral RNA as collected via self-administered nasopharyngeal swabs may be evidence of an infection it does not provide any information of the infectivity of a person, i.e. his or her ability to transmit the virus to other persons. To better understand these data the two following aspects should be clarified post-authorisation: 1) The Ct values for subjects with asymptomatic SARS-CoV-2 infection should be submitted, and it should be clarified whether the viral load, in case of asymptomatic infection, was impacted by vaccination; and 2) an estimate of the relative frequency of asymptomatic versus symptomatic infections in each study arm should be provided (acknowledging that observation-time would need to be equalized, and that symptomatic and asymptomatic infections are likely to be competing events).

Ancillary analyses

The presence of comorbidities at baseline did not have an impact on the vaccine efficacy against COVID-19 disease in seronegative subjects, which was similar to healthier participants. Generally, this result fits with the expectation that the most common respiratory or cardiovascular comorbidities represented in the trial are not expected to have an impact on the immune response. Immunosuppressed patients were excluded.

Among participants older than 65 years of age, 2 and 6 cases of COVID-19 were reported for the vaccine (≥15 days post dose 2) and control, respectively. Vaccine efficacy could thus not be demonstrated as too few COVID-19 cases were reported. This is the result of low recruitment in these subjects as well as of less follow

up time since they were recruited later than younger adults based on a safety risk-adverse age escalation strategy. Since older adults are at higher risk of severe complications following SARS-CoV-2 infection, this limitation is reflected in the SmPC.

Similarly, fewer participants were recruited in the age range 56 to 65 years of age, so that no efficacy estimate could be obtained in this age subgroup. Among participants aged between 56 and 65 years old, 8 cases of COVID 19 were reported in those receiving the vaccine (≥15 days post dose 2) compared with 9 cases for control.

Protection after first dose

Insight into vaccine efficacy between the first and second dose is particularly relevant considering the variable dosing interval proposed and the intended use within a pandemic, where there is a need to achieve protection as soon as possible. In this case the dose interval ranges up to 12 weeks, with the possibility that vaccine efficacy may be already waning at the end of this interval before the second dose has been received. Several exploratory subgroup analyses were conducted based on the 7 December data cut off in an attempt to estimate the protective efficacy during this interval. Examination of the Cumulative Incidence curves indicates that induction of protective immunity started 21 days after the first dose, which is biologically plausible.

The pooled VE in the time period starting 21 days after dose 1 until dose 2 (censored at 12 weeks post dose 1) in subjects who received SD/SD is estimated at 73.2% (95% CI: 54.3, 84.3). It should be noted however that efficacy estimates vary between trials since in COV002 VE for the same interval is 44% (95% CI: -66.8, 81.3) whereas in trial COV003 it is 80% (95% CI: 55.3, 91.2). Relevantly, in COV003 the median interval between dose 1 and dose 2 is only 5 weeks, while in COV002 the median interval was 10 weeks. The UK study would therefore be best suited to study the maintenance of protection during the longer time interval up to 12 weeks, however, few cases were accrued as during this interval the attack rate was low. The Brazil study provided higher estimates of protection, but most of the COVID19 cases occurred during the first few weeks after vaccination. A pooled estimate, which appears to be driven mainly by observations from the early peak of cases in the Brazil study, cannot be generalized to the full duration of 12 weeks between the first and second dose. A number of additional uncertainties further hamper the interpretation of the pooled estimate, for example the studies were not designed to estimate vaccine efficacy after first dose. In addition, similar or higher vaccine efficacy estimates are seen when measured from 22 days post dose-1 or 14 days post dose-2, with overlapping confidence intervals, making interpretation of numerical differences difficult. Therefore, the exact level of protection induced by one dose of COVID-19 Vaccine AstraZeneca over the full 12 weeks interval cannot be reliably estimated based on the available data.

The KM curves show a persistent effect up to 12 weeks.

Overall the results show that the first SD dose provides protective immunity starting 3 weeks after the first dose and although the exact level of protection cannot be reliably estimated protection persists up to 12 weeks, as seen when the second dose was administered at longest time intervals. A second dose is required and is considered important for immune consolidation and long-term protection.

Duration of protection after the second dose

Duration of protection is at the moment unknown. The applicant has been asked to pre-specify how waning of vaccine efficacy will be studied post-authorisation as follow-up time accumulates, especially regarding how the likely unblinding and crossover to the alternative arm will be accounted for.

Use of Paracetamol

Paracetamol use was not consistently measured in COV002 and COV003 studies, and it is not possible to understand the impact of paracetamol on efficacy, if any. However based on the available immunogenicity data an effect is considered unlikely.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for studies COV001, COV002, COV003 and COV005 will be submitted no later than May 2022. The primary analysis based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies will be submitted no later than March 2021 and May 2022 respectively.

In order to confirm the efficacy of AZD1222 in the elderly and subjects with underlying disease, the overview and summaries of the primary analysis and final clinical study report for study D8110C00001 will be submitted no later than April 2021 and March 2024 respectively. These datasets are subject to specific obligations laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Although several aspects of the clinical development have challenged the interpretation of the data (e.g. the wide and variable interval between the 2 doses, the administration of 2 different regimens LD/SD and SD/SD), the overall conclusion is that AZD1222, when given as a 2 standard dose regimen, provides protection against symptomatic COVID-19.

Since the VE efficacy results for the LD/SD regimen are difficult to interpret due to a number of confounding factors, the SD/SD subset is considered to reflect more closely the VE expected from field vaccination. Further, the data assessed support the posology as proposed by the Applicant of two doses administered between 4 and 12 weeks.

Vaccine efficacy in the SD/SD seronegative efficacy set (4-12 weeks) was 59.5 (95% CI: 45.8, 69.7).

AZD122 provides protections against severe COVID-19, ICU and hospital admission, however no reliable efficacy estimate could be obtained for the time being due to the low number of cases.

Evidence of efficacy of AZD1222 against asymptomatic SARS-CoV-2 infection was not observed also due to the low number of cases reported.

Currently available clinical trial data do not allow an estimate of vaccine efficacy in subjects over 55 years of age. This is especially important for elderly subjects aged 65 years or older, who are at risk for severe COVID-19 and who may be affected by immunosenescence. However, based on comparable immunogenicity vs. younger adults, it is possible to infer protection in individuals >65YOA.

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing studies.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should submit

the final Clinical Study Reports for the randomised, controlled studies COV001, COV002, COV003 and COV005.

- In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should provide the primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.
- In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.

2.6. Clinical safety

2.6.1. Methodology

Safety data were collected from four studies, COV001, COV002, COV003 and COV005 and a pooled analysis of these data has been presented. The collection methods varied between the studies.

In COV001, COV002, and COV003, solicited events were collected for 8 days (i.e., day 0–7) compared to 7 days in COV0005 study (i.e., day 0-6).

The collection and definitions of solicited AEs were not identical between studies: Studies COV001 and COV002 have identical diaries, and the diary for COV003 is very similar and contributed data from 7 local events and 10 systemic events, while study COV005 contributed data from only 5 local events and 5 systemic events. Further, in COV005, different Severity Grades Scale for fever, Redness, Swelling and Induration were employed. Moreover, Feverishness and chills, in COV005, were reported without severity grading. Due to differences in collection of reactogenicity data in COV005, pooling of reactogenicity data from all four studies was not agreed. Therefore reactogenicity data is based on the pooled reactogenicity set from COV001, COV002 and COV003.

The occurrence of unsolicited adverse events was recorded for 28 days after any dose and information on SAEs and AESIs was planned to be collected for the entire study period. As the list of AESIs changed considerably during the course of the trials, it is possible that there is underreporting of AESIs that are non-serious and occur more than 28 days after any dose.

There was no specific guidance in the protocols on how to assess relatedness of AEs and it was left to the discretion of the investigator.

Further, it should be noted that in the control group in the AZD1122 trials the subjects were administered the MenACWY vaccine or saline, which complicates the comparison of the data between AZD1222 and control arms.

2.6.2. Patient exposure

The assessment of AZD1222 safety is based on the interim analysis of the results from all studies pooled in the total Safety analysis Set, comprising 23,745 participants (12,021 subjects: any dose of AZD1222, 11,724: control vaccine or placebo). Among the 12,021 subjects, dose 1 SD was given to 10,069 subjects and dose 1 LD to 1,947 subjects. A two-dose study intervention regimen was received by approximately two-thirds of participants. In the AZD1222 group, most participants had received two doses of the SD/SD regimen

(54.6%) or a single SD before the data cut-off (28.7%). Note that five patients randomised to control received AZD1222 as their second vaccination. These 5 patients are included in the AZD1222 group of the Any Dose for Safety Analysis Set but are excluded from both the Dose 1 SD for Safety Analysis Set and Dose 1 LD for Safety Analysis Set.

In the Any Dose for Safety Analysis set, the median number of days of follow up from the first dose was 105 days in the AZD1222 treatment group and 104 days in the control group. The median follow up in the Dose 1 SD Safety analysis set was 90 days in the AZD1222 group and 89 days in the control group from the first dose. The maximum duration of follow up was 196 days from the first dose. The median of duration of follow up from the second dose was 55.6 days in AZD1222 and 54.7 days in control group (Any dose for Safety Analysis Set). In the Any Dose for Safety Analysis set, which comprises all subjects receiving at least one LD or SD of AZD1222, the median number of days of follow up since the first dose was similar between the AZD1222 treatment group (105.0 days) and the control group (104.0 days).

For the reactogenicity assessment, a subset of 3,203 subjects receiving any dose of AZD1222 (SD and LD pooled) and 2,934 receiving a control vaccine was analysed. Of these 3,203, a total of 2,648 participants received SD and 553 received LD as a first dose. Further, 986 participants were enrolled in COV005. COV005 was excluded from the pooled reactogenicity set as reactions were solicited with different methods.

The applicant clarified on request that the selection of subjects for the immunogenicity analysis set was based on a pragmatic approach. This is not considered a random selection, which probably explains the imbalances between the treatment groups in terms of demographics and baseline characteristics. As these imbalances are small, no substantial impact on treatment differences is expected.

Demographic and baseline characteristics were generally similar among participants who received AZD1222 and the control treatment in the Any dose Safety analysis. Overall, the demographic characteristics (age, sex race) are similar in the Any dose and in the Dose 1 safety analysis sets.

In the Any dose Safety Analysis Set, 91.1%of the participants were aged 18 to 64 years, and 8.9% of participants aged 65 years or older. Overall, in the safety population, 55.8% were female, 44.1% were male, 75.7% were White, 10.2% were Black, 4.1% were mixed race, 3.4% were Asian, and 6.5% were reported to be of other races.

Most participants (95.1%) were seronegative at baseline. Approximately one-third of participants had comorbidity at baseline (35.8%). The demographic and baseline characteristics were generally similar among participants that received AZD1222 and the control treatments.

The studies excluded pregnant/breastfeeding women, participants with severe immunodeficiency, or participants with severe underlying disease. Regarding HIV participants, they were included in COV002 and COV003 studies but excluded from the pooled analysis. A safety analysis of HIV population is lacking; therefore it is included as missing information in the RMP.

2.6.3. Adverse events

Solicited AEs

Solicited AEs were collected in a subset of 2,648 subjects receiving Dose 1 SD for 7 days following each vaccination. An overview of solicited local reactions by dose is presented for the pooled Dose 1 SD safety set in Table 33 below. An overview of systemic reactions can be found in Table 34.

Any local and systemic AE were reported more frequently in AZD1222 than in control group (86% and 71.7% of evaluated participants), within the first 7 days following any dose of AZD1222 or control treatment, respectively.

Solicited local and systemic AEs were generally milder and reported less frequently after the second dose than after first dose of AZD1222.

The mean duration of local reactions in the AZD1222 group was 3.3 days after the first dose, compared to 2.3 days in the control group. For systemic reactions, the mean duration was 2.8 days after the first dose, compared to 2.6 days in the control group. After the second dose the mean duration was 2.3 and 2.7 days in the AZD1222 group for local and systemic reaction compared to 2.0 and 2.5 days in the control group respectively. By dose, the reactogenicity of AZD1222 was lower in participants in the < 6 weeks dosing interval compared with participants in the > 6 weeks dosing intervals. The frequency of local and systemic solicited AEs after the first vaccination (in Dose 1 SD for Safety analysis Set) was numerically lower in the subgroup with dosing interval < 6 weeks (56% and 59%, respectively) as compared to the subgroup with dosing interval > 6 weeks (72% and 71%, respectively). A larger proportion (85%) of older adults received their second dose < 6 weeks after their first vaccination (overall, older adults reported reduced reactogenicity). The differences observed after the first dose and after the second vaccination with a dosing window < 6 weeks may reflect potential differences in the population studied or other confounding factors. Thus, interpretation of an effect due to dose interval should be undertaken with caution.

Table 33 Summary of Local Solicited Adverse Events Post Any Dose, Post Dose 1 or Post Dose 2 (Dose 1 SD for Safety Analysis Set: COV001, COV002, COV003 Pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**
Participants with any local solicited AE									
Any	1466 (84.4)	930 (62.1)	59 (59.6)	1410 (81.9)	844 (57.0)	58 (59.2)	482 (58.6)	329 (48.1)	5 (21.7)
Mild	1212 (69.8)	823 (55.0)	52 (52.5)	1169 (67.9)	763 (51.6)	51 (52.0)	458 (55.7)	295 (43.1)	5 (21.7)
Moderate	240 (13.8)	101 (6.7)	6 (6.1)	227 (13.2)	77 (5.2)	6 (6.1)	24 (2.9)	31 (4.5)	0
Severe	14 (0.8)	6 (0.4)	1 (1.0)	14 (0.8)	4 (0.3)	1 (1.0)	0	3 (0.4)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Pain									
Any	941 (54.2)	530 (35.4)	56 (56.6)	889 (51.6)	457 (30.9)	55 (56.1)	221 (26.9)	164 (24.0)	5 (21.7)
Mild	776 (44.7)	471 (31.5)	51 (51.5)	729 (42.3)	413 (27.9)	50 (51.0)	212 (25.8)	145 (21.2)	5 (21.7)
Moderate	156 (9.0)	56 (3.7)	5 (5.1)	151 (8.8)	42 (2.8)	5 (5.1)	9 (1.1)	18 (2.6)	0
Severe	9 (0.5)	3 (0.2)	0	9 (0.5)	2 (0.1)	0	0	1 (0.1)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Tenderness									
Any	1307 (75.3)	812 (54.2)	32 (32.3)	1243 (72.2)	727 (49.1)	32 (32.7)	420 (51.0)	291 (42.5)	1 (4.3)
Mild	1153 (66.4)	752 (50.2)	31 (31.3)	1098 (63.8)	685 (46.3)	31 (31.6)	404 (49.1)	271 (39.6)	1 (4.3)
Moderate	146 (8.4)	56 (3.7)	1 (1.0)	137 (8.0)	39 (2.6)	1 (1.0)	16 (1.9)	18 (2.6)	0
Severe	8 (0.5)	4 (0.3)	0	8 (0.5)	3 (0.2)	0	0	2 (0.3)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Redness									
Any	51 (2.9)	28 (1.9)	2 (2.0)	44 (2.6)	24 (1.6)	2 (2.0)	7 (0.9)	4 (0.6)	0
Mild (2.5–5 cm)	34 (2.0)	13 (0.9)	0	29 (1.7)	10 (0.7)	0	5 (0.6)	3 (0.4)	0
Moderate (5.1–10 cm)	15 (0.9)	13 (0.9)	1 (1.0)	13 (0.8)	13 (0.9)	1 (1.0)	2 (0.2)	0	0

Table 33 Summary of Local Solicited Adverse Events Post Any Dose, Post Dose 1 or Post Dose 2 (Dose 1 SD for Safety Analysis Set: COV001, COV002, COV003 Pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**
Severe (>10 cm)	2 (0.1)	2 (0.1)	1 (1.0)	2 (0.1)	1 (0.1)	1 (1.0)	0	1 (0.1)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Warmth									
Any	308 (17.7)	222 (14.8)	10 (10.1)	272 (15.8)	189 (12.8)	10 (10.2)	71 (8.6)	64 (9.4)	0
Mild	301 (17.3)	215 (14.4)	8 (8.1)	266 (15.4)	185 (12.5)	8 (8.2)	70 (8.5)	61 (8.9)	0
Moderate	7 (0.4)	7 (0.5)	2 (2.0)	6 (0.3)	4 (0.3)	2 (2.0)	1 (0.1)	3 (0.4)	0
Severe	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Itch									
Any	120 (6.9)	82 (5.5)	3 (3.0)	100 (5.8)	67 (4.5)	3 (3.1)	30 (3.6)	17 (2.5)	0
Mild	114 (6.6)	79 (5.3)	3 (3.0)	96 (5.6)	65 (4.4)	3 (3.1)	28 (3.4)	16 (2.3)	0
Moderate	6 (0.3)	3 (0.2)	0	4 (0.2)	2 (0.1)	0	2 (0.2)	1 (0.1)	0
Severe	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Swelling									
Any	51 (2.9)	31 (2.1)	3 (3.0)	46 (2.7)	27 (1.8)	3 (3.1)	7 (0.9)	6 (0.9)	0
2.5–5 cm and no IwA	33 (1.9)	19 (1.3)	0	29 (1.7)	17 (1.1)	0	6 (0.7)	3 (0.4)	0
5.1–10 cm or IwA	16 (0.9)	12 (0.8)	3 (3.0)	15 (0.9)	10 (0.7)	3 (3.1)	1 (0.1)	3 (0.4)	0
>10 cm or PDA	2 (0.1)	0	0	2 (0.1)	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Induration									

Table 33 Summary of Local Solicited Adverse Events Post Any Dose, Post Dose 1 or Post Dose 2 (Dose 1 SD for Safety Analysis Set: COV001, COV002, COV003 Pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**
Any	49 (2.8)	32 (2.1)	2 (2.0)	45 (2.6)	26 (1.8)	2 (2.0)	5 (0.6)	11 (1.6)	0
2.5–5 cm and no IwA	41 (2.4)	26 (1.7)	0	37 (2.1)	21 (1.4)	0	5 (0.6)	9 (1.3)	0
5.1–10 cm or IwA	6 (0.3)	6 (0.4)	2 (2.0)	6 (0.3)	5 (0.3)	2 (2.0)	0	2 (0.3)	0
>10 cm or PDA	2 (0.1)	0	0	2 (0.1)	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23

Control A: MenACWY (meningococcal group a, c, w-135, and y conjugate vaccine)
Control B: MenACWY (first dose) and Saline Placebo (second dose)
In COV001 and COV002 a total of 32 participants received SDLD dosing.
The number of participants evaluated for each solicited AE category (ie, "N evaluated" in the table) was used as the denominator in the percentage calculations.
If a participant reported more than one occurrence of the same event, the event of greatest intensity was included in the analysis.
Solicited AEs were assessed daily after vaccination from Day 0 to Day 7 via e-diary or diary card.
For Redness and Swelling, severity grading was derived based on reported value.
AE = Adverse Event; ED = Exfoliative dermatitis; ER=Emergency department; IwA = Interfere with activity; PDA = Prevent daily activity.
Source: AZD1222: Table 1.5.1.2.2 IEMT 126. Control A: Table 3.5.1.2.2.a. Control B: Table 3.5.1.2.2.b.

Table 34 Summary of Systemic Solicited Adverse Events Following Any Dose, Dose 1 or Dose 2 (Dose 1 SD for Safety Analysis Set, COV001, COV002, COV003 pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002**
Participants with any systemic solicited AE									
Any	1411 (81.3)	1040 (69.5)	64 (64.6)	1361 (79.0)	962 (65.0)	63 (64.3)	469 (56.0)	326 (47.2)	5 (21.7)
Mild	696 (40.1)	745 (49.8)	40 (40.4)	697 (40.5)	717 (48.4)	40 (40.8)	347 (41.4)	242 (35.1)	3 (13.0)
Moderate	553 (31.9)	270 (18.0)	23 (23.2)	514 (29.8)	227 (15.3)	22 (22.4)	107 (12.8)	77 (11.2)	2 (8.7)
Severe	162 (9.3)	25 (1.7)	1 (1.0)	150 (8.7)	18 (1.2)	1 (1.0)	15 (1.8)	7 (1.0)	0

Table 34 Summary of Systemic Solicited Adverse Events Following Any Dose, Dose 1 or Dose 2 (Dose 1 SD for Safety Analysis Set, COV001, COV002, COV003 pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002**
ER or hospi-talisation	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	838	690	23
Fever									
Any	159 (9.2)	8 (0.5)	0	156 (9.1)	6 (0.4)	0	4 (0.5)	3 (0.4)	0
38.0 – 38.4°C	95 (5.5)	7 (0.5)	0	95 (5.6)	6 (0.4)	0	1 (0.1)	2 (0.3)	0
38.5 – 38.9°C	52 (3.0)	0	0	50 (2.9)	0	0	2 (0.2)	0	0
39.0 – 40°C	12 (0.7)	1 (0.1)	0	11 (0.6)	0	0	1 (0.1)	1 (0.1)	0
>40°C	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1710	1469	98	838	690	23
Feverishness									
Any	583 (33.6)	153 (10.2)	18 (18.2)	546 (31.7)	122 (8.2)	17 (17.3)	79 (9.6)	39 (5.7)	1 (4.3)
Mild	270 (15.6)	138 (9.2)	15 (15.2)	246 (14.3)	113 (7.6)	14 (14.3)	62 (7.5)	32 (4.7)	1 (4.3)
Moderate	252 (14.5)	13 (0.9)	3 (3.0)	241 (14.0)	8 (0.5)	3 (3.1)	15 (1.8)	6 (0.9)	0
Severe	61 (3.5)	2 (0.1)	0	59 (3.4)	1 (0.1)	0	2 (0.2)	1 (0.1)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Chills									
Any	554 (31.9)	125 (8.4)	7 (7.1)	535 (31.1)	101 (6.8)	7 (7.1)	42 (5.1)	32 (4.7)	0
Mild	278 (16.0)	109 (7.3)	6 (6.1)	265 (15.4)	89 (6.0)	6 (6.1)	32 (3.9)	26 (3.8)	0
Moderate	216 (12.4)	16 (1.1)	1 (1.0)	212 (12.3)	12 (0.8)	1 (1.0)	8 (1.0)	6 (0.9)	0
Severe	60 (3.5)	0	0	58 (3.4)	0	0	2 (0.2)	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Joint pain									
Any	469 (27.0)	163 (10.9)	9 (9.1)	423 (24.6)	129 (8.7)	8 (8.2)	85 (10.3)	46 (6.7)	1 (4.3)
Mild	336 (19.4)	134 (9.0)	8 (8.1)	299 (17.4)	104 (7.0)	7 (7.1)	72 (8.7)	40 (5.8)	1 (4.3)

Table 34 Summary of Systemic Solicited Adverse Events Following Any Dose, Dose 1 or Dose 2 (Dose 1 SD for Safety Analysis Set, COV001, COV002, COV003 pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002**
Moderate	119 (6.9)	26 (1.7)	1 (1.0)	110 (6.4)	22 (1.5)	1 (1.0)	13 (1.6)	6 (0.9)	0
Severe	14 (0.8)	3 (0.2)	0	14 (0.8)	3 (0.2)	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Muscle pain									
Any	843 (48.6)	365 (24.4)	23 (23.2)	782 (45.4)	314 (21.2)	22 (22.4)	180 (21.9)	92 (13.5)	1 (4.3)
Mild	567 (32.7)	324 (21.6)	20 (20.2)	527 (30.6)	283 (19.1)	19 (19.4)	150 (18.2)	80 (11.7)	1 (4.3)
Moderate	246 (14.2)	40 (2.7)	3 (3.0)	225 (13.1)	30 (2.0)	3 (3.1)	30 (3.6)	12 (1.8)	0
Severe	30 (1.7)	1 (0.1)	0	30 (1.7)	1 (0.1)	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Fatigue									
Any	1082 (62.3)	719 (48.0)	29 (29.3)	1017 (59.1)	642 (43.4)	27 (27.6)	313 (38.0)	208 (30.4)	2 (8.7)
Mild	662 (38.1)	535 (35.7)	22 (22.2)	633 (36.8)	485 (32.8)	20 (20.4)	238 (28.9)	164 (24.0)	2 (8.7)
Moderate	361 (20.8)	172 (11.5)	7 (7.1)	331 (19.2)	148 (10.0)	7 (7.1)	68 (8.3)	41 (6.0)	0
Severe	59 (3.4)	12 (0.8)	0	53 (3.1)	9 (0.6)	0	7 (0.9)	3 (0.4)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Headache									
Any	999 (57.5)	635 (42.4)	46 (46.5)	936 (54.4)	564 (38.1)	46 (46.9)	268 (32.6)	171 (25.0)	4 (17.4)
Mild	653 (37.6)	514 (34.3)	32 (32.3)	618 (35.9)	479 (32.4)	33 (33.7)	220 (26.7)	130 (19.0)	2 (8.7)
Moderate	305 (17.6)	114 (7.6)	14 (14.1)	280 (16.3)	79 (5.3)	13 (13.3)	45 (5.5)	40 (5.8)	2 (8.7)
Severe	41 (2.4)	7 (0.5)	0	38 (2.2)	6 (0.4)	0	3 (0.4)	1 (0.1)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Malaise									
Any	768 (44.2)	295 (19.7)	28 (28.3)	703 (40.8)	238 (16.1)	27 (27.6)	147 (17.9)	79 (11.5)	1 (4.3)
Mild	417 (24.0)	232 (15.5)	20 (20.2)	375 (21.8)	196 (13.2)	19 (19.4)	108 (13.1)	56 (8.2)	1 (4.3)

Table 34 Summary of Systemic Solicited Adverse Events Following Any Dose, Dose 1 or Dose 2 (Dose 1 SD for Safety Analysis Set, COV001, COV002, COV003 pooled)

	Post Any Dose, n (%) of participants			Post Dose 1, n (%) of participants			Post Dose 2, n (%) of participants		
Parameter	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002)**	**AZD1222 (N = 9083)**	**Control A (N = 3917)**	**Control B (N = 5002**
Moderate	285 (16.4)	56 (3.7)	8 (8.1)	268 (15.6)	38 (2.6)	8 (8.2)	32 (3.9)	20 (2.9)	0
Severe	66 (3.8)	7 (0.5)	0	60 (3.5)	4 (0.3)	0	7 (0.9)	3 (0.4)	0
ER or hospi-talisation	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Nausea									
Any	380 (21.9)	197 (13.2)	12 (12.1)	348 (20.2)	162 (10.9)	12 (12.2)	69 (8.4)	56 (8.2)	0
Mild	291 (16.8)	163 (10.9)	10 (10.1)	264 (15.3)	140 (9.5)	10 (10.2)	60 (7.3)	44 (6.4)	0
Moderate	74 (4.3)	33 (2.2)	1 (1.0)	72 (4.2)	22 (1.5)	1 (1.0)	6 (0.7)	11 (1.6)	0
Severe	15 (0.9)	1 (0.1)	1 (1.0)	12 (0.7)	0	1 (1.0)	3 (0.4)	1 (0.1)	0
ER or hospi-talisation	0	0	0	0	0	0	0	0	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23
Vomiting									
Any	29 (1.7)	12 (0.8)	2 (2.0)	24 (1.4)	10 (0.7)	2 (2.0)	5 (0.6)	3 (0.4)	0
Mild	14 (0.8)	7 (0.5)	1 (1.0)	11 (0.6)	6 (0.4)	1 (1.0)	3 (0.4)	2 (0.3)	0
Moderate	9 (0.5)	4 (0.3)	0	9 (0.5)	4 (0.3)	0	0	0	0
Severe	6 (0.3)	1 (0.1)	1 (1.0)	4 (0.2)	0	1 (1.0)	2 (0.2)	1 (0.1)	0
N evaluated	1736	1497	99	1722	1480	98	823	684	23

Control A: MenACWY (meningococcal group a, c, w-135, and y conjugate vaccine)
Control B: MenACWY (first dose) and Saline Placebo (second dose)
In COV001 and COV002 a total of 32 participants received SDLD dosing.
The number of participants evaluated for each solicited AE category (ie, "N evaluated" in the table) was used as the denominator in the percentage calculations.
If a participant reports more than one occurrence of the same event, then the event of greatest intensity is included in the analysis.
Solicited AEs were assessed daily after vaccination from Day 0 to Day 6 for COV005 and to Day 7 for rest of studies via e-diary or diary card.
AE = Adverse Event, ER=Emergency department.
Source: AZD1222 data: Table 1.5.1.3.2 IEMT 126. Control A: Table 3.5.1.3.2.a. Control B: Table 3.5.1.3.2.b.

The most frequently reported solicited local AEs after any dose SD of AZD1222 were tenderness (75.3% vs 54.2% in subjects who received MenACWY) and pain (54.2% vs 35.4% in control); other solicited local AEs were reported in ≥10% of AZD1222 participants. Severe local reactions were experienced by 0.8% of subjects

The most frequently reported solicited systemic AEs after any dose SD of AZD1222 were fatigue (62.3% vs 48.0% in subjects who received MenACWY as control) and headache (57.5% vs 42.4% in control); other frequently reported systemic solicited AEs were muscle pain (48.6%), and malaise (44.2%). Pyrexia was reported in 9.2% participants who received any dose of AZD1222 (vs 0.5% in control). Most of the systemic AEs following AZD1222 were mild or moderate. However, an 9.3% of subjects experienced grade 3 systemic AEs, being malaise, chills and feverishness the most frequently grade 3 solicited systemic AE reported. A single Grade 4 event was reported after the first dose in the AZD1222 group for fever (i.e., > 40°C).

Unsolicited AEs

In the Dose 1 SD for Safety Analysis Set, 40.1% of participants in the AZD1222 group and 29.4% of participants in the control group reported an unsolicited AE within 28 days following any dose. Similarly, all the unsolicited AEs after any dose considered as related to the study vaccine were reported in a higher percentage than comparator (32.3% vs 20.0% respectively). Nonetheless, a reduction of the unsolicited AEs percentages (related or not) after the second dose was observed in both the study vaccine and the comparator (34.8% post dose 1 and 11.4% post dose 2 in AZD1222 participants vs 23.6% post dose 1 and 9.3% post dose 2 in control group). Most AEs were mild to moderate in severity.

The most frequently reported unsolicited AEs predominantly occurred within ≤7 days of any dose. When reported by PT, they were consistent with AEs commonly observed following vaccination: vaccination site pain, headache, pyrexia and myalgia. There were not unsolicited AEs reported by preferred term ≥2% within 8-28 days after any dose either AZD1222 or control group.

A similar pattern to unsolicited AE was observed for unsolicited related AEs by SOC in Any Dose for safety analysis Set (see table below), Dose 1 SD or Dose 1 LD for Safety Set. The most frequently reported unsolicited related AEs by SOC (Any Dose for Safety analysis Set) were included under the SOC General disorders and administration site conditions (23.4%), nervous system disorder (9.3%) and Musculoskeletal and connective tissue disorders (2.7%) in AZD1222. The frequencies were higher in AZD1222 than in control group (12.8%, 5.5%, 1.6%, respectively).

Lymphadenopathy was reported for 32 subjects (0.3%) in both the AZD1222 group as well as the control group; 'lymph node palpable' was reported for one subject in both groups (Any Dose for Safety Analysis Set). Considering the related AEs, lymphadenopathy was considered at least possibly related by the investigator for 24 cases following vaccination with AZD1222.

Table 35 Investigational Product Related Unsolicited Adverse Events by System Organ Class (Any Dose for Safety Analysis Set)

	AZD1222 (N = 12021)	Control (N = 11724)
Participants with any investigational product Related Unsolicited AE	3570 (29.7)	2172 (18.5)
System organ class uncoded	65 (0.5)	42 (0.4)

Infections and infestations	68 (0.6)	70 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	
Blood and lymphatic system disorders	28 (0.2)	28 (0.2)
Immune system disorders	3 (< 0.1)	1 (< 0.1)
Metabolism and nutrition disorders	30 (0.2)	13 (0.1)
Psychiatric disorders	28 (0.2)	14 (0.1)
Nervous system disorders	1117 (9.3)	644 (5.5)
Eye disorders	32 (0.3)	19 (0.2)
Ear and labyrinth disorders	8 (0.1))	18 (0.2)
Cardiac Disorders	13 (0.1)	3 (< 0.1)
Vascular disorders	34 (0.3)	32 (0.3)
Respiratory, thoracic and mediastinal disorders	128 (1.1)	121 (1.0)
Gastrointestinal disorders	323 (2.7)	184 (1.6)
Skin and subcutaneous tissue disorders	118 (1.0)	73 (0.6)
Musculoskeletal and connective tissue disorders	1081 (9.0)	448 (3.8)
Renal and urinary disorders	3 (< 0.1)	2 (< 0.1)
Reproductive system and breast disorders	5 (< 0.1)	4 (< 0.1)
General disorders and administration site conditions	2813 (23.4)	1505 (12.8)
Investigations	96 (0.8)	31 (0.3)
Injury, poisoning and procedural complications	11 (0.1)	10 (0.1)
Social circumstances	1 (<0.1)	

Related = possible, probably or definitely related according to the investigator. Source: Table 1.5.2.5.1 Investigational Product Related Unsolicited Adverse Events by System Organ Class and Preferred Term (Any Dose for Safety Analysis Set)

An imbalance in the frequency of unsolicited AEs reported in the SOC Nervous System Disorders between AZD1222 and the control groups is observed. In the Any dose safety set, there were 1,408 events (11.7 %) reported in the AZD1222 group vs. 918 (7.8%) in the control group. The PTs included headache, lethargy, migraines, somnolence, and dizziness. There were also 2 events of loss of consciousness in the AZD1222 and none in the control group. Further, the frequency of related unsolicited AEs by SOC Nervous System Disorders is higher in the AZD1222 group (1,117 events or 9.3%) than in the control (644 events or 5.5%). From these 9.3% related AES by SOC Nervous System Disorders in AZD1222, 6.4% were Grade 1 and 2.7% were Grade 2. There were few Grade 3 (0.2%) and Grade 4 (< 0.1%) events. However, in general the related AEs grades 2-4 were slightly more frequent in the AZD1222 group.

Most unsolicited Nervous System Disorders AEs were reported in the first 7 days. The frequency of AEs in this category post day 7 was lower than in the first 7 days, and similar in both AZD1222 and control groups (AZD1222 2.1%; control, 1.9%).

The most common adverse event reported in the SOC of Nervous system disorder is Headache and the majority of the events of headache were considered as related by the investigator (7.9% in the AZD1222 group vs 4.5% in the control group) and is listed as an ADR for AZD1222 in section 4.8. Other PTs that were reported in this SOC with a frequency of more than 0.1% and that were more frequently reported in the AZD1222 than in the control arm are Dizziness, Lethargy, Migraine and Somnolence.

Headache, fatigue, lethargy or paraesthesia had a median duration of up to seven days. Other related AEs including ageusia and similar, anosmia and neuralgia lasted 7-21 days; facial paralysis (SAE), myelitis transverse (SAE), dysesthesia and sensory loss and disturbance lasted up to 3 months.

There were six cases of facial paralysis in the Any dose safety set, three in the AZD1222 group and three in the control. For one case in the AZD1222 group, based on the timing, relatedness to the vaccine cannot be excluded and this event is considered at least possibly related to vaccination. The participant was treated and the outcome is unknown. The two other cases had features suggesting they were not related to AZD1222 vaccination (one case is considered related to mastoiditis and MRI finding of a rare condition; the other occurred 80 days after vaccination). In the control group, one case was deemed possibly related to vaccination due to the timing of the event (day of vaccination).

Based on the review of the severity and duration of the related nervous system disorders events, a possible causal relationship between AZD122 and some events in the SOC of Nervous System Disorders cannot be ruled out A potential risk of nervous system disorders including immune mediated conditions is included in the RMP.

2.6.4. Serious adverse event/deaths/other significant events

Overall, the incidence of SAEs was low and similar in the AZD1222 and control groups. Less than 1% of participants from the safety population or from any subgroup reported an SAE. The most frequently reported SAEs by SOC in the AZD1222 and groups were Infections and Infestations (0.1% and 0.2% of participants respectively) and Injury, Poisoning and Procedure Related Complications (0.1% in both groups). Less than 0.1 % participants reported a SAE considered treatment related by the investigator, 3 in the AZD1222 group (pyrexia, elevated C-reactive protein, and myelitis transverse) and 2 in the control (autoimmune haemolytic anaemia and myelitis), although, after the cut-off date, causality for the SAE of C-reactive protein increased was updated by the investigator to not treatment related.

There was an imbalance in the number of SAEs by SOC Nervous System Disorders (7 events in the AZD1222 group vs. 4 events in the control group in the Any dose safety analysis) (see the following paragraph).

There were 6 deaths (2 in the AZD1222 and 4 in the control groups) none related to the study intervention.

Adverse events of special interest

The overall incidence of AESIs was low: 0.8 % of participants in the AZD1222 group (95 cases) and 1.1 % in the control group (126 cases). There were 30 participants (0.2%) in the AZD1222 group and 44 (0.4%) in the control group who reported AESIs considered related by the investigator.

The majority of the reported events were paraesthesia, hypoesthesia and muscular weakness that account for 57 of 95 AESIs in the AZD1222 and 76 of 126 cases in the control group.

Within 28 days after vaccination 33 cases (0.3%) of Paraesthesia were reported in the AZD1222 group compared to 34 cases (0.3%) in the control group in the Any Dose for Safety Analysis Set. Of these 15 (0.1%) and 19 (0.2%) cases were considered related to the study intervention, respectively. The majority of the cases were mild to moderate in severity (only 1 case of Grade 3 in AZD1222). After this 28 day period of follow-up, 4 additional cases were reported in AZD1222 and 14 cases in the control group.

Overall, there was no imbalance between the two groups, and the numbers of related cases were limited. Furthermore, the number of cases of Dysesthesia, Hypoesthesia and Hyperaesthesia was low in both groups.

Although hypoesthesia is listed in the SmPC for one of the meningococcal vaccines used as control in the clinical trials, Nimenrix, it is not included for Menveo and neither have included paraesthesia.

In conclusion, it was considered that a causal relationship between AZD1222 and Paraesthesia/ Hypoesthesia / Dysesthesia could not be established and paraesthesia should not be added as an ADR in the SmPC.

Three AESIs in total were reported as SAEs: transverse myelitis, myelitis and multiple sclerosis. In both the AZD1222 and the control groups, other SAEs reported in the Nervous System Disorders SOC were: Facial spasm, Migraine, Ischaemic stroke, Presyncope, syncope, Serotonin syndrome, subarachnoid haemorrhage and transient ischaemic attack). The SAEs ischaemic stroke, migraine, subarachnoid haemorrhage, transient ischaemic attack, syncope and presyncope may have cardiovascular aetiology. , After reviewing the narratives of the SAEs in this SOC and given the proximity in time to vaccination, it is considered that only two SAEs (Facial spasm and migraine) may be potentially related to study treatment.

The SAE of Multiple sclerosis was considered unrelated to study treatment according to the neurologist assessment, as the MRI showed new and pre-existent brain lesions. Therefore .it was considered that the biological process leading up to the symptoms preceded study treatment administration.

In addition, in the ongoing US phase 3 clinical trial D8110C00001, which is not included in the CMA, two SAEs one of Peripheral Sensory neuropathy and one event of Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) have been reported.

The incidence of CIDP has been estimated to around 0.33 per 100,000 person-year (Broers et al, Neuroepidemiology 2019;52:161–172). Based on the narrative it is not possible to exclude causality with study intervention nor to confirm it. The Investigator considered the SAE to be related to study intervention.

Regarding the event of Peripheral Sensory Neuropathy, relatedness is unclear.

Further, there was a case of acute encephalopathy in the COVISHIELD study (study not included in the current application for CMA) which is suspected to be a nutritional encephalopathy, however an autoimmune aetiology has not been ruled out.

A single case of a non-serious event of anaphylactic reaction was reported, which is considered not related to study treatment. At least one additional case of a potential hypersensitivity reaction has been noted in the safety database, a subject who experienced erythema multiforme, tongue swelling and urticaria popular, whose relatedness is doubtful. Relevantly, subjects with a history of allergic reactions (angioedema, anaphylaxis or allergic disease or reactions that could possibly be exacerbated by any component of AZD1222, MenACWY or paracetamol) were excluded from participation in the studies. Therefore, it may be that more immunologic reactions will be observed if the vaccine is used in the general public.

2.6.5. Laboratory findings

Regarding the clinical laboratory results in the AZD1222 group, these were within normal clinical range and did not raise any safety concerns.

2.6.6. Safety in special populations

The solicited and unsolicited AEs were less frequently reported in adults aged ≥65 years receiving any AZD1222 vaccine than in adults aged 18-64 years, however the population aged ≥65 years included in the assessment is much smaller than the group of adults aged 18-64 years**.**

Regarding participants with comorbidity at baseline, a safety pooled analysis has been provided showing a similar safety profile of AZD1222 in participants with and without comorbidities at baseline. Moreover, a subgroup analysis of safety stratified by different comorbidities (BMI > 30kg/m2, cardiovascular disorder, respiratory disease, or diabetes) has been provided throughout the rolling review procedure. The data have shown, overall, no imbalances in the incidence of solicited AEs, unsolicited AEs, SAEs and AESIs for any of the comorbidities, being very similar among participants in the different subgroups.

Overall, slightly lower frequencies of solicited AEs were reported in seropositive than seronegative participants at baseline, for both AZD1222 and control groups. However, severity of the local AEs was observed in higher percentages in the seropositive population receiving AZD1222. Considering that the number of participants of seropositive exposed to AZD1222 is very low, these results should be interpreted with caution.

When analysing the reactogenicity profile of AZD1222 across countries, less frequent local and systemic AEs were reported in South Africa than in UK or Brazil, in both AZD1222 and control groups. These lower rates could be due to the difference in the solicited events recorded in the patient diaries and the different number of days for collection of the solicited AEs in the South Africa Study, as explained by the Applicant.

Moreover, after updating the frequencies of severe solicited local and systemic AEs by the Applicant the difference observed between South African and UK or Brazil studies was less pronounced. Unsolicited AEs were most frequently reported in Brazil as 98% of participants may have reported typical reactogenicity AEs as unsolicited AEs.

In general, no imbalances were observed between special populations, such as: age, comorbidity, country or serostatus regarding SAEs or AESIs.

Regarding pregnant women, within the clinical trials submitted there were 10 pregnancies in subjects exposed to AZD1222, and 7 exposed to the control. It is not entirely clear if in all cases women were already pregnant at the time of exposure to the vaccine, however it is plausible. The outcome for 8/10 pregnancies in the AZD1222 group is not yet known. For 4 of 7 women exposed to the control, the outcome of pregnancy is known and considered normal. No safety signals based upon the above information are identified; however the information is still extremely limited.

The use of AZD1222 in pregnant and breastfeeding women will be investigated in the planned PASS activities. This is considered relevant and is endorsed, although an important risk is not expected.

2.6.7. Immunological events

The immunologic events were pre-specified as AESIs.

2.6.8. Safety related to drug-drug interactions and other interactions

No interaction studies have been performed.

Concomitant administration of AZD1222 with other vaccines has not been studied.

Based on the results from 56 and 57 participants (AZD1222 and control groups respectively) receiving prophylactic paracetamol, in the COV001 phase 1 study, the reactogenicity (local and systemic) within two days after vaccination might be reduced in participants receiving AZD1222, although the number of participants is too small to make a solid conclusion.

In COV002 and COV003 studies, very limited information regarding use of prophylactic paracetamol was provided. There was a recommendation for prophylactic paracetamol to be administered before vaccination and participants were advised to use 1 gram of paracetamol every 6 hours for 24 hours to reduce vaccine-associated reactions. There were higher rates of solicited AEs in those participants who reported prophylactic paracetamol use than in those who did not report prophylactic paracetamol use. The interpretation of this data warrants caution, and the higher rates of solicited reactogenicity in those receiving paracetamol prophylaxis suggests that paracetamol was taken in response to symptoms and that truly prophylactic use was rare.

Prophylactic paracetamol use was not captured in the participant diary for study COV005.

2.6.9. Discontinuation due to adverse events

From the Any dose for safety analysis set, 133 (0.6%) participants discontinued early from the study. The reason for discontinuing was Adverse event in one participant (<0.1%) in control group and non-related deaths in 5 participants (<0.1%) in both groups. Other reasons were: Exclusion criteria met, lost to follow-up, withdrawal by the subject and other causes.

No information has been presented on the number of subjects that did not receive a second dose due to an Adverse Event following the first dose. Whilst there are several indications in individual narratives that this may have been the case, it appears this information has not been collected systematically.

2.6.10. Post marketing experience

There are no post-marketing data as the vaccine. AZD1222 vaccine has only recently been granted emergency approval in several countries (e.g., UK).

2.6.11. Discussion on clinical safety

Exposure

The assessment of AZD1222 safety is based on the interim analysis of the results from all studies pooled in the total Safety analysis Set, comprising 23,745 participants (12,021 subjects: any dose of AZD1222, 11,724: control vaccine or placebo) from four individual studies, COV001, COV002, COV003 and COV005. Slight differences regarding the methodology for collection of AEs and the measurement of the severity scale between trials were observed. Due to differences between the methods applied in COV005 compared with the other studies, information relating to solicited AEs from COV005 should not be pooled with the other studies.

Reactogenicity were collected in a subset of 2,648 participants receiving Dose 1 SD for 7 days following each vaccination, and 553 receiving dose 1 of LD. As 986 participants were enrolled in COV005, these were excluded from the pooled reactogenicity subset.

Among the 12,021 participants, dose 1 SD was given to 10,069 subjects and dose 1 LD to 1,947 subjects. A two-dose study intervention regimen was received by approximately two-thirds of participants. In the AZD1222 group, most participants had received two doses of the SD/SD regimen (54.6%) or a single SD before the data cut-off (28.7%).

In the Any Dose for Safety Analysis set, the median number of days of follow up was 105 days in the AZD1222 treatment group and 104 days in the control group from the first dose. The median exposure in the Dose 1 SD Safety analysis set was 90 days in the AZD1222 group and 89 days in the control group. The maximum duration of follow up was 196 days from the first dose. The median of duration of follow up from the second dose was 55.6 days in AZD1222 and 54.7 days in control group (Any dose for Safety Analysis Set).

Demographic and baseline characteristics were generally similar among participants who received AZD1222 and the control treatment in the Any dose Safety analysis. 8.9% of participants were aged 65 or older. Most participants (95.1%) were seronegative at baseline. Approximately one-third of participants had at least one comorbidity at baseline (35.8%). The demographic characteristics (age, sex, race) are similar for the any dose and the Dose 1 SD safety analysis set.

HIV participants were included in COV002 and COV003 studies but excluded from the pooled analysis. A safety analysis of HIV population is lacking; therefore it is included as missing information in the RMP.

Adverse events

Solicited AEs, unsolicited AEs, SAEs (including deaths) and AESIs were evaluated.

Solicited Adverse Events: Any local and systemic AE were reported more frequently in AZD1222 than in control group. Solicited local and systemic AEs were generally milder and reported less frequently after the second dose than after first dose of AZD1222. By dose interval, the reactogenicity of AZD1222 was lower in participants in the < 6 weeks dosing interval compared with participants in the > 6 weeks dosing intervals, however this may have been confounded by differences in the population studied or other factors. Thus, interpretation of an effect due to the dose interval should be undertaken with caution.

The most frequently reported solicited local AEs in AZD1222 group were tenderness, followed by pain. The most frequently reported solicited systemic AEs in AZD1222 group were fatigue and headache, followed by muscle pain, malaise, feverishness, chills, joint pain and nausea.

Unsolicited Adverse events: Any unsolicited AEs were reported more frequently in AZD1222 group than in control treatment and generally reflected reactions to vaccination such as vaccination site pain, headache, pyrexia and myalgia. A majority of events was mild to moderate in severity, showing a reduction of the percentages (related or not) after the second dose in both the study vaccine and the comparator. The most frequently reported unsolicited AEs predominantly occurred within ≤7 days of any dose. There were no unsolicited AEs reported by preferred term in more than 2% of subjects within 8-28 days after any dose either AZD1222 or control group.

A noticeable imbalance in the frequency of unsolicited AEs in the Nervous System Disorder class between the AZD1222 and the control group is observed in the pooled results for the any dose safety analysis set. Further, the imbalance is also present in the reported unsolicited AEs related to the ADZ1222 vaccine.

There were 3 cases of facial paralysis in the AZD1222 group and 3 in the control group. For one of the cases in the AZD1222 group, causality to the vaccine could not be excluded. There was no imbalance between the study groups in the occurrence of Bell's palsy. No risk is identified as only a single case occurred for which

causality to the vaccine cannot be determined. Facial paralysis is however considered an adverse event of special interest (AESI) and will be characterized in the planned PASS studies and other ongoing clinical studies. A targeted questionnaire will be utilized for adverse reaction follow-up as a part of routine pharmacovigilance activities post-authorisation.

AESIs: The overall incidence of AESIs was low: 0.8 % of participants in the AZD1222 group (95 cases) and 1.1 % in the control group (126 cases). The majority of the reported events were paraesthesia, hypoesthesia and muscular weakness that account for 57 of 95 AESIs in the AZD1222 and 76 of 126 cases in the control group. There were 30 participants (0.2%) in the AZD1222 group and 44 (0.4%) in the control group who reported AESIs considered related by the investigator.

There was no imbalance of paraesthesia, dysesthesia, Hypoesthesia and Hyperaesthesia between the two groups, and the numbers were limited. The causal relationship with AZD1222 could not be established.

Three AESIs in total were reported as SAEs across treatment groups, of which transverse myelitis and myelitis were considered possibly related to the intervention by the investigator although causation could not be established, and multiple sclerosis was considered unlikely related to the intervention. The SAEs facial spasm and migraine, belonging to the same CNS SOC, may be potentially related to the intervention.

In the US study DC8110C00001 an additional two events which were AESIs and serious were reported: an event of sensory neuropathy and an event of Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP). Further, a case of acute encephalopathy was reported in the COVISHIELD study, which is a suspected nutritional encephalopathy, but other aetiologies have not been ruled out.

It is uncertain whether the study treatment was the cause of any of these events.

Based on the reported neurological AEs and SAEs after vaccination with AZD1222, it is proposed that any serious or severe events within the SOC of Nervous System disorders, including those of immunological origin, are included for close follow up in the RMP via routine and additional pharmacovigilance activity.

Further, due to the potential auto-immune aetiology in two events, the applicant is requested to investigate whether there may be potential molecular mimicry between the viral vector and human (neurologic) tissue. To this end, the applicant may perform a Basic Local Alignment Search Tool (BLAST) search.

There was one case of anaphylaxis 63 days after vaccination which is not related to AZD1222. Relevantly, subjects with a history of allergic reactions (angioedema, anaphylaxis or allergic disease or reactions possibly exacerbated by any component of AZD1222, MenACWY or paracetamol) were excluded from participation in the studies. Therefore it may be that more immunologic reactions will be observed if the vaccine is used in the general public. Anaphylaxis has been included as a safety concern in the Safety Specification, and a warning is included in 4.4 to alert health care providers to this potential risk.

SAEs: Overall, the incidence of SAEs was low (less than 1%) and similar in the AZD1222 and control groups. The most frequently reported SAEs by SOC in the AZD1222 and groups were Infections and Infestations (0.1% and 0.2% of participants respectively) and Injury, Poisoning and Procedure Related Complications (0.1% in both groups). There were 2 SAEs considered treatment related by the investigator in the AZD1222 group and 2 in the control (pyrexia, autoimmune haemolytic anaemia and myelitis).

There were 6 deaths (2 in the AZD1222 and 4 in the control groups), none related to the study intervention.

Safety by subgroup

The solicited and unsolicited AEs were less frequently reported in adults aged ≥65 years receiving any AZD1222 vaccine than in adults aged 18-64 years. Considering that the population aged ≥65 included for the assessment is much smaller than the group of adults aged 18-64, more data from older participants are needed to make any comparison on reactogenicity in the different age groups.

Regarding participants with comorbidity at baseline, a safety pool analysis has been provided showing a similar safety profile of AZD1222 in participants with and without comorbidities at baseline. Moreover, a subgroup analysis of safety stratified by different comorbidities (BMI ≥30kg/m2, cardiovascular disorder, respiratory disease, or diabetes) showed overall no imbalances in the incidence of solicited AEs, unsolicited AEs, SAEs and AESIs for any of the comorbidities.

Overall, slightly lower frequencies of solicited AEs were reported in seropositive than seronegative participants at baseline, for both AZD1222 and control groups. However, the severity of the local AEs was observed in higher percentages in the seropositive population receiving AZD1222. Considering that the number of participants of seropositive exposed to AZD1222 is very low, these results should be interpreted with caution.

When analysing the reactogenicity profile of AZD1222 across countries, less frequent local and systemic AEs were reported in South Africa than in UK or Brazil, in both AZD1222 and control groups. There were slight differences in the percentage of severe solicited local and systemic AEs reported after receiving the AZD1222 in the South African population than in the UK or Brazil studies. Unsolicited AEs were most frequently reported in Brazil as 98% of participants may have reported typical reactogenicity AEs as unsolicited AEs.

In general, no imbalances were observed between special populations, such as: age, comorbidity, country or serostatus regarding SAEs or AESIs.

There is only very limited clinical experience in pregnant women, with 14 pregnant women in the safety database who were exposed to AZD1222. Use of AZD1222 in pregnant and breastfeeding women will be investigated in the planned PASS activities.

Additional safety data needed in the context of a conditional MA

The final clinical study report for studies COV001, COV002, COV003 and COV005 will be submitted no later than May 2022. The primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies will be submitted no later than March 2021 and May 2022 respectively.

In order to confirm the safety of AZD1222 in the elderly and subjects with underlying disease, the overview and summaries of the primary analysis and final clinical study report for study D8110C00001 will be submitted no later than April 2021 and March 2024 respectively. These datasets are subject to specific obligations laid down in the MA.

2.6.12. Conclusions on the clinical safety

The safety of AZD1222 is mainly characterised by local and systemic reactions occurring during the first 7 days after vaccination. Reactions were mostly mild to moderate and were self-limiting. Nonetheless, they were reported less frequently after the second dose than after first dose of AZD1222. Less frequently solicited AEs were reported in adults aged ≥ 65 than adults aged 18-65. There were no difference in the

safety profile between seropositive and seronegative participants at baseline.

There were a few nervous system disorders including neuro-inflammatory events for which potential causal relationship to vaccination could not be established, and which need to be followed post-authorisation. However, no specific risk has been identified.

In conclusion, the observed safety profile is considered as favourable.

Data are limited or lacking in the following population, which are addressed by adequate measures detailed in the RMP (see section 2.7):

- Use during pregnancy and while breastfeeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
- Use in patients with autoimmune or inflammatory disorders
- Interactions with other vaccines

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional marketing authorisation:

- Long term safety data (final clinical study reports for studies COV001, COV002, COV003, COV005 and D8110C00001, see section 4).

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Table 36: Summary of safety concerns

Important identified risks	None
Important potential risks	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis

Missing information	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety

Risks considered important for inclusion of the summary of safety concerns

Based on the reported neurological events in clinical trials possibly related to the AZD1222, it is proposed that *Nervous system disorders, including immune-mediated neurological conditions* is included as an important potential risk, and closely followed up via routine and additional pharmacovigilance activities: follow-up questionnaire to be used for immune-mediated events, ongoing clinical trials and post-marketing observational studies.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) are taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it from spontaneous reports (follow-up questionnaire) and studies: ongoing clinical trials and post-marketing observational studies.

No related case of anaphylaxis was reported in clinical trials; considering the experience with other vaccines, that the vaccine is a biological product, and the pandemic mass vaccination circumstances, anaphylaxis was added as an important potential risk. A follow-up questionnaire will be used to collect further information following spontaneous reports.

Missing information

Information on safety of use during pregnant or while breastfeeding is extremely limited, as those populations were excluded from the clinical trials. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

Data from use in frail patients with co-morbidities is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies and an ongoing and a new clinical trial.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is requested. The Applicant will investigate the co-administration of Comirnaty with other vaccines as part of the enhanced active surveillance study and as part of the observational study using existing secondary health data sources.

At the data cut-off of, 13-15 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the clinical trials and the PASS.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

The theoretical concern that the vaccine could induce HLA sensitisation in transplant candidates and recipients is not supported by the investigations of the vaccine content that showed no evidence of HLA proteins in the product, and by the serum sample testing from vaccinated individuals that showed no de-novo occurrence of anti-HLA antibodies following vaccination. Therefore, it is considered acceptable that this theoretical concern is not included in the list of safety concerns in the RMP.

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine surveillance activities to specifically address the challenges in the context of the pandemic are described below.

Signal detection

Routine signal detection activities will be supplemented by qualitative and quantitative methods, using different sources of data.

The sources of data for signal detection and frequency of review are as followed:

- AstraZeneca global safety database (SAPPHIRE), which includes clinical trial SAEs and post-marketing case reports received by the Applicant and from other sources (e.g. MHRA, EudraVigilance) – weekly review,
- EudraVigilance Data Analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR) – bi-weekly review,
- US Vaccine Adverse Event Reporting System (VAERS) – weekly review,
- Literature (Embase and Insight Meme) – weekly review,
- All clinical trial AEs from AZ and non-AZ sponsored studies – bi-weekly review,
- Batch distribution data – monthly review.

The methods used for signal detection include disproportionality analyses in different databases (i.e. SAPPHIRE, VAERS and EudraVigilance), routine safety data review, batch-related adverse reactions analysis, O/E analysis using background rates from ACCESS and other sources, ad hoc time-series analysis and ad hoc cluster analysis. Time-to onset analysis is currently under evaluation.

ICSR reporting

All ICSRs received for AZD1222 will be processed and reported in accordance with the requirements specified in the EMA guidance document entitled 'Detailed Guidance on ICSRs in the context of COVID-19 - Validity and coding of ICSRs (EMA/174312/2020)' (EMA 2020c).

Specific adverse reaction follow-up questionnaires

Targeted follow-up questionnaires will be in place for important potential risks and AESIs. Applicable targeted follow-up questionnaires for 'COVID-19/ Vaccine Failure and Vaccine-Associated Enhanced Disease (VAED)', 'Anaphylaxis' and 'Immune-mediated neurological conditions' (i.e. important potential risks) are provided in Annex 4 of the RMP.

Monthly Summary Safety Reports

In addition to the submission of Periodic Safety Update Reports (PSURs) at 6-monthly intervals, Summary Safety Reports will be produced at monthly intervals for AZD1222. The key content of each report will be as defined below:

- Estimated exposure from post-marketing experience (if possible stratified by sex and age)
- Data in Summary Tabulations:
    - Reference information
    - Cumulative and interval summary tabulations (by HLT and SOC)
    - Overview of data presented in tabulations (AESIs, safety concerns, vaccination errors, and batch analysis)
- Summary of ongoing and closed validated signals
- Changes to Reference Safety Information
- Summary of significant findings from clinical trials during the reporting period
- Health Authority Requests
- Late-breaking Information
- Conclusion and actions (reflecting risk-benefit considerations)

With regards to AESIs, safety concerns and fatal AEs, the total number of any such events will be discussed in the context of O/E analyses, which will be conducted as part of signal detection activities.

Traceability

In order to facilitate traceability of batch numbers for pharmacovigilance, stickers detailing relevant brand name and batch numbers will be placed into all cartons of drug product at the Contract Manufacturing Organizations (CMO) packing sites. Two stickers will be provided per dose, hence, for both HCP and patient records. The stickers will include the vaccine name (i.e., '*COVID-19 Vaccine AstraZeneca*'), the relevant batch number, and a 2D barcode. Initial batches will include stickers without 2D barcode, for a period of maximum two weeks after the approval.

Traceability instructions for HCPs are provided in the SmPC.

Traceability and Vaccination reminder cards will be available for vaccinators to facilitate batch number traceability. These cards are designed to be completed at the time of vaccination and be given to the vaccinee. The use of these cards is left to Member States decision. The Traceability and Vaccination reminder cards will contain the following elements:

- Placeholder space for name of vaccinee
- Vaccine brand name and manufacturer name
- Placeholder space for due date and actual date of first and second doses, and space for batch/lot number
- A reminder to retain the card and to bring it to the appointment for the second dose of the vaccine; in addition to a reminder to save the card after the second dose
- QR code that links to an MAH website with additional information on product use
- Placeholder for AE reporting information (national contact points)

At the time of initial vaccine availability, sufficient quantities of blank Traceability and Vaccination cards will be provided to vaccinators in Member States will require it. These cards will also be made available on the Applicant websites, where permitted by National Competent Authorities.

The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number and expiry date, which can be used for trackability.

Additional pharmacovigilance activities

The applicant proposed five non-interventional studies (4 safety and 1 effectiveness), and eight interventional studies to identify and characterise the risks of the product. The non-interventional studies are all planned and classified as category 3 PASS. Seven interventional studies are ongoing; five of them are specific obligations (category 2) and two trials are classified as category 3 studies. One interventional study is planned in immunocompromised patients, classified as a category 3 study.

Table 37: Additional pharmacovigilance activities

Activity type and description **Status**	**Study name/code**	**Summary of activity objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - *Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation*					
None					
Category 2 – *Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances*					

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Study COV001 A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers • **Status**: Ongoing	• COV001	*Primary Objectives:* To assess efficacy of AZD1222 against COVID-19 To assess the safety of AZD1222 *Key secondary Objectives:* To assess the reactogenicity profile of AZD1222 To assess cellular and humoral immunogenicity of AZD1222	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Final report	Q1 2022
Study COV002 A Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 • **Status**: Ongoing	• COV002	*Primary Objectives:* To assess efficacy and safety of AZD1222 against COVID-19 in adults aged 18 years and older in the UK *Secondary Objectives:* To assess the reactogenicity profile of AZD1222 To assess efficacy of AZD1222 against severe and non-severe COVID-19 To assess humoral immunogenicity of AZD1222 To assess cellular immunity of AZD1222 in older adults To assess the safety and immunogenicity of a booster dose of AZD1222 in older adults aged 56 years or older (two-dose schedule).	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Final report	Q2 2022
Study COV003 A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1	• COV003	*Primary Objective:* To evaluate the efficacy of AZD1222 vaccine against COVID-19 disease confirmed with PCR *Secondary Objectives:* To evaluate the safety, tolerability and reactogenicity profile of AZD1222 To evaluate the efficacy of AZD1222 against severe and non-severe COVID-19 disease To evaluate the humoral immunogenicity of AZD1222 To assess the cellular immunogenicity of AZD1222.	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Final report	Q2 2022

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
nCoV-19 Vaccine • **Status**: Ongoing					
Study COV005 An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non-Replicating ChAdOx1 SARS-CoV-2 Vaccine in South African Adults Living Without HIV, and Safety and Immunogenicity in Adults Living with HIV • **Status**: Ongoing	• COV005	*Primary Objective:* To assess the safety of AZD1222 in healthy HIV-uninfected adults To assess efficacy of AZD1222 against COVID-19 To assess the safety of the candidate vaccine AZD1222 in adults living with HIV To evaluate the immunogenicity of AZD1222 after first and second doses of vaccine in adults living with HIV *Secondary Objectives:* To assess the immunogenicity of AZD1222 in healthy HIV-uninfected adults.	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Use in immunocompromised patients Long-term safety	Final report	Q2 2022
D8110C00001 A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector	• D8110C00001	*Primary Objectives:* To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only) *Key Secondary Objectives:* To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Interim analysis	Q1 2021

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Vaccine, for the Prevention of COVID-19 **Status**: Ongoing		CDC criteria To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits			

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - *Required additional pharmacovigilance activities*					
Enhanced active surveillance A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222 • **Status**: Planned	• D8111R00003 (EU) • D8110R00001 (US) • ESR 21-21121 (UK; DSRU-sponsored))	*Primary Objectives:* To assess the safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 3 months after vaccination with the first dose of AZD1222. *Secondary Objectives:* To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 for 18 months after vaccination To assess the safety and tolerability of AZD1222 in participants ≥ 65 year of age and in other key subgroups. To estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date. To estimate the frequency of select outcomes in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated date of conception.	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Use during pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interactions with other vaccines Long-term safety	Study Design Concept submission	11 Dec 2020
				Protocol submission for review	28 Jan 2021
				Final protocol submission	23 Feb 2021
				Start of study	18 May 2021
				First interim report	Q3 2021
AZD1222 Pregnancy Registry Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy • **Status**: Planned	• *Study code to be confirmed*	*Primary Objectives:* To estimate the risk of selected adverse pregnancy outcomes (ie, spontaneous abortions, stillbirths, and preterm births) in women receiving at least 1 dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP To estimate the risk of selected adverse foetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 12 months of life (to account for diagnosis of major congenital malformations that might be delayed) in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP.	Use during pregnancy and while breastfeeding	Initial Study Design Concept submission	11 Dec 2020
				Protocol submission	27 Jan 2021

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Post-marketing observational study using existing secondary health data sources A post-authorisation /post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns. • **Status**: Planned	• *Study code to be confirmed* (US) • D8111R00006 (EU/UK)	<u>*Primary Objectives*</u>*:* To estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222, among all populations targeted for vaccination and in the specific populations considered as missing information To estimate the relative risk (comparing exposed and unexposed person time) of safety concerns including AESIs among all populations targeted for vaccination and in the specific populations considered as missing information To characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Use during pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interactions with other vaccines Long-term safety	Study Design Concept submission	18 Dec 2020
				Protocol submission	01 Apr 2021
Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency • **Status**: Planned	• *Study code to be confirmed*	<u>*Primary objective:*</u> To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	Use in immunocompromised patients	Study protocol submission	01 Nov 2021

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Interventional study in immunocompromised subjects • **Status**: Planned	• *Study code to be confirmed*	*Primary objective:* To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	Use in immunocompromised patients	Protocol submission	28 Feb 2021
Post-marketing effectiveness study Post-authorisation / Post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public-private partnership with COVIDRIVE utilizing primary data collected prospectively through the COVIDRIVE platform. **Status**: Planned	• D8111R00005 (EU/UK) • *Study code to be confirmed* (US)	*Primary Objective:* To estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 in hospitalized patients, overall and by age group (< 18, 18-64 and ≥ 65 years old), after adjusting for potential confounders.	*Not applicable*	Protocol submission	Directed by COVI-DRIVE consortium, expected March 2021

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Study COV004 A Phase IB/II Single-Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya • **Status**: Ongoing	• COV004	*Primary Objectives:* To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 To assess immunogenicity of ChAdOx1 nCoV-19 *Secondary Objectives:* To assess humoral immunogenicity of ChAdOx1 nCoV-19 at early and late timepoints To assess cellular immunogenicity of ChAdOx1 nCoV-19 To assess efficacy of ChAdOx1 nCoV-19 against COVID-19	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Final report	2022
D8111C00002 A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19 • **Status**: Ongoing	• D8111C00002	*Primary Objectives:* To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo. To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222. *Secondary Objectives:* To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo. To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay) To assess the function of nAb against SARS-CoV-2 spike protein To assess the safety of the candidate vaccine AZD1222. To describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo. To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.	Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long-term safety	Interim analysis Primary analysis	Q1 2021 Q2 2021

Routine pharmacovigilance activities are considered sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

Routine Risk Minimisation Measures

Potential medication errors

As AZD1222 will initially be administered in large scale vaccination programmes, there is a potential to introduce the risk of vaccination errors. Vaccination errors may relate to administration, vaccination scheme, storage conditions, or errors associated with multi-dose vials. These potential vaccination errors will be mitigated through a number of strategies:

- SmPC Section 6.6 contains instructions on administration and storage conditions for AZD1222. Instructions on vaccination scheme are provided in SmPC Section 4.2.
- HCP and the public guides have been prepared, which include specific sections on AZD1222 administration and storage.
- Medical information call centres are available for the public and HCPs to respond to questions about AZD1222.
- Traceability and Vaccination reminder cards will be provided where applicable.

Furthermore, as other COVID-19 vaccines are also available, there is the potential for confusion or interchangeability with other COVID-19 vaccines. The above tools will facilitate the education of HCPs on the avoidance of this situation.

Summary of additional risk minimisation measures

None proposed.

Table 38: Summary of pharmacovigilance and risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Nervous system disorders, including immune-mediated neurological conditions	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire (to be sent for immune-mediated neurological conditions only) **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anaphylaxis	**Routine risk communication*:*** • SmPC Sections 4.3 and 4.4 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Missing Information		
Use during pregnancy and while breastfeeding	**Routine risk communication*:*** • SmPC Section 4.6 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • AZD1222 Pregnancy Registry • Post-marketing observational study using existing secondary health data sources
Use in immunocompromised patients	**Routine risk communication*:*** • SmPC Section 4.4 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study COV005 • EAS • Post-marketing observational study using existing secondary health data sources • Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency • Interventional study in immunocompromised patients
Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients with autoimmune or inflammatory disorder	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources
Interactions with other vaccines	**Routine risk communication:** • SmPC Section 4.5 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources
Long-term safety	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002

Conclusion

The CHMP and PRAC considered that the risk management plan version 1 / succession 5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, during the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29 December 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

AZD1222 is a recombinant chimpanzee adenovirus expressing the severe acute respiratory syndrome-coronavirus-2 (SARS CoV2) Spike (S) surface glycoprotein with a tissue plasminogen activator (tPA) leader sequence. There are no mutations introduced in the expressed SARS-CoV-2 Spike protein of AZD1222.

The applicant declared that Chimpanzee adenovirus encoding the SARS-CoV-2 spike glycoprotein (ChAdOx1-S) has not been previously authorised in a medicinal product in the European Union.

The active substance for this product is considered to be the entire chimpanzee adenovirus encoding the SARS-CoV-2 spike glycoprotein (ChAdOx1-S) and given that no products have been authorised in the EU with this AS, the applicant's position is agreed.

The CHMP, based on the available data, considers SARS-CoV-2 spike glycoprotein (ChAdOx1-S) to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable, given the current urgent public health need for rapid development and approval of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease, and because the product will always be administered by a healthcare professional.

The applicant is expected to thoroughly review and update the package leaflet in the light of the results from the user testing.

2.10.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[2] document which aims at facilitating the preparedness work of COVID-19

[2] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

EU packaging specific derogations

a) Outer and immediate labelling in English only

Outer and immediate labelling will be provided in English only for all EU Member States, as well as Norway and Iceland.

Country/language specific outer/immediate labelling will be provided in all EU languages by 2nd quarter 2022.

This exemption is justified on the necessity to provide maximum flexibility of supply and speed of vaccine production/deployment due to the ongoing pandemic. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. The use of unified English-only pack components will allow the vaccine to be distributed across multiple countries simultaneously. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

Additionally, a QR code and URL printed on the outer carton and the patient information leaflet (PL) will provide access to the product information in the national language(s).

b) Printed package leaflet

From the beginning of supply and until end of March 2021

No printed package leaflet (PL) will be supplied to EU MSs, including Norway and Iceland. During this time access to the national version of the PL will only be available via a QR code/URL printed on the outer carton and on vaccination reminder cards, where available. The company shall work with MSs on national solutions, if possible, where printed cards are not available.

This exemption is justified on the necessity to accelerate launch activities of the first batches of the vaccine following EC decision due to the ongoing pandemic.

From end of March 2021 until 2nd quarter 2022

The MAH shall supply as of end of March 2021 a printed package leaflet in the national language(s) of the following MSs: Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an English-only PL, will receive the English printed PL. This exemption is justified to minimise delays in release of the vaccine to countries as supply will be equitable across the EU markets. Production of PLs in different languages will significantly reduce the supply chain efficiency due to constraints at the print vendors and complex logistics. Keeping the number of different language printed PLs to a minimum increases the printing capacity, simplifies the logistics at the distribution hubs and facilitates a rapid deployment to multiple markets simultaneously.

In addition, a QR code/URL printed on the outer carton and the PL will provide access to the package leaflet in the national language(s).

The MAH shall ensure a 1:1 supply of printed PL to dose of vaccine. Moreover, the MAH shall contact MSs directly to agree on the exact numbers of PLs to be distributed in line with the published Q&A on labelling

flexibilities.

From 2nd quarter 2022

The MAH shall provide a printed package leaflet in all EU languages by 2nd quarter 2022. The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned, as well as to agree on the exact numbers of PLs to be distributed in line with the published Q&A on labelling flexibilities.

c) Outer and immediate labelling. Temporary omission of certain particulars on the labelling (from start of supply to end May 2021).

The following exemption is temporarily agreed for the outer labelling. This exemption is justified on the necessity to label batches ahead of time.

Outer carton

- Pharmaceutical form: 'solution for injection' (initially proposed), instead of 'suspension for injection' (agreed during evaluation)

d) Statement of active substance

Due to the expedited development, product specifications were not final at the early stage of printing packaging materials. Therefore, the statement of active substance will be fully omitted from the outer carton for the first batches.

From end of May 2021

As of end May 2021 the statement of the active substance on the outer carton will be implemented as follows: `One dose (0.5 ml) contains not less than 2.5×10^8 infectious units´

Due to space constraints and in order to ensure readability it has been allowed to omit permanently the sentence: `Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S´ from the carton.

e) EU Marketing Authorisation number (from start of supply to end of May 2021)

Due to the expedited development, the EU number was not available at the early stage of printing packaging materials, and hence it will not appear on the initial launch components.

The inclusion of the EU Marketing Authorisation number in the labelling will be implemented by end May 2021.

f) Blue Box (from start of supply to 2nd quarter 2022)

Due to the use of one unified pack across all the EU countries, an exemption for the Blue Box is requested for omission from the outer carton.

The information normally provided in the market specific packaging Blue Box area of the carton will be provided as an electronic version on the website (via the QR code/URL) under the country page, if required by the National Competent Authorities in each MS.

The Blue Box will be included in the updated carton component when national variants of the packaging will be possible by 2nd Quarter 2022.

2.10.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

Statutory information

- Approved regulatory information, including the patient information leaflet (PIL) and Summary of Product Characteristics (SmPC).
- Traceability and Vaccination Reminder Card.
- Blue Box information as required by each Member State

Additional information

- Link to the national reporting systems for adverse events websites
- Local telephone numbers for safety reporting
- Product Quality Complaints via electronic reporting form to AstraZeneca

2.10.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COVID-19 Vaccine (ChAdOx1-S [recombinant]) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.11. Compliance with scientific advice

The Applicant has followed the previous CHMP recommendations with regards to some critical methodological issues, including planning for a minimum statistical success criteria to be based on the superiority of the lower bound of the VE multiplicity adjusted confidence interval to a 20% threshold, restricting the primary analysis to patients with a negative serostatus at baseline and the confirmation that the clinical studies would continue after any interim analysis despite reaching statistical significance.

Evidence of efficacy for AZD1222 at CMA is based on pooled data from Studies COV002 and COV003; these studies are included in the pooled interim analysis for efficacy based on having met the predetermined criterion of at least 5 cases of COVID-19. Evidence of immunogenicity and safety for AZD1222 is based on pooled data from all 4 studies.

The strategy for pooling of data across studies, vaccination regimens and dose, was extensively discussed and agreed (with caveats) in previous advices. The main points that stand out compared to the advices is the strength of evidence supporting administration in elderly (6% accrual of subjects aged 65+ years vs. ≥25% recommended in advices) and the unexpected, at the time of advice, trend for higher immunogenicity and efficacy following the LD-SD compared to SD-SD dose regimen.

3. Benefit-Risk Balance

3.1.1. Disease

The claimed indication for AZD1222 vaccine is active immunisation of individuals ≥18 years of age to prevent coronavirus disease 2019 (COVID-19). COVID-19 is a respiratory disease caused by the novel coronavirus SARS-CoV-2. The virus has spread worldwide during 2020, causing WHO to declare a pandemic in March 2020. The virus infects the airways and causes a broad spectrum of respiratory symptoms ranging from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS) and ARDS. The pandemic is still ongoing despite unprecedented efforts to control the outbreak.

3.1.2. Available therapies and unmet medical need

Only a couple of medicinal products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (remdesivir) and anti-inflammatory therapy (dexamethasone). A number of products are in clinical development, either antivirals such as monoclonal antibodies directed against the spike protein, convalescent plasma/hyperimmune immunoglobulins or anti-inflammatory medicinal products. Other widely used treatments for hospitalised patients include anticoagulants. These therapies have shown variable efficacy depending on the severity and duration of illness.

While care for individuals with COVID-19 has improved with clinical experience gained over time, there remains an urgent and unmet need for vaccines able to prevent or mitigate COVID-19 during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired.

There are currently two mRNA vaccines in the EU to prevent COVID-19 approved as conditional marketing authorisation. In addition, several vaccine programs are ongoing globally. There is a very high global demand for suitable vaccines to help counteract the ongoing pandemic.

3.1.3. Main clinical studies

This application is based on 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). Participants received AZD1222 or control (COV001, COV002 used MenACWY vaccine as first and second dose. COV003 used MenACWY vaccine as first dose and saline as second dose; COV005 used saline for both).

Evidence of efficacy for AZD1222 is based on pooled data from studies COV002 and COV003 because these studies met the predetermined criterion of having accrued at least 5 cases of COVID-19. Evidence of immunogenicity and safety for AZD1222 is based on data from all 4 studies.

The studies were designed to demonstrate efficacy against PCR-confirmed COVID-19 disease with at least one of the following symptoms: fever (≥37.8°C), cough, shortness of breath, anosmia or ageusia.

Overall, based on the DCO 4 November 2020, a total of 23,753 subjects were randomized 1:1 to receive AZD1222 vaccine or a control (either MenACWY vaccine or saline). The pooled analysis set for safety was composed of 23,745 subjects and the efficacy analysis set included 20,014 participants. The efficacy analyses were updated with the DCO of 7 December and included 12,196 seronegative participants who received 2 standard doses of AZD1222 vaccine (SD/SD) at any dose interval.

The efficacy analysis was event-driven, and the efficacy pooled analysis (based on 7 December cut-off) was based on 322 adjudicated cases of confirmed COVID-19 that occurred ≥15 days post second dose (LDSD + SDSD seronegative for efficacy analysis set, any dosing interval), of which 218 cases occurred in participants who received the SD/SD regimen across the AZD1222 and control groups in pooled studies. Evidence of immunogenicity and safety for AZD1222 is based on data from all 4 studies based on a data cut off of 4 November. Follow-up of participants is expected to continue until study end to provide an estimate of the durability of protection.

3.2. Favourable effects

The efficacy of the AZD1222 vaccine according to the prespecified primary analysis set was 66.5% (95% CI: 56.9, 73.9) against COVID-19 in seronegative participants at baseline who received SD/SD or LD/SD and with a follow-up ≥15 days post second dose. The primary objective was met since the lower bound of the 95% CI of vaccine efficacy was above 20%.

The primary efficacy analysis included participants who received the intended SD/SD dose regimen, but also participants who received an accidental low dose as the first dose (LD/SD regimen). When the decision was made to switch to a two-dose regimen, the protocol specified to give them at least 4 weeks apart. Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 23 weeks (21 to 159 days), with 86.1% of participants receiving their two doses within the interval of 4 to 12 weeks (28 to 84 days). In COV002, the second dose was received ≥12 weeks after the first for 71.2% of subjects who received LD/SD compared to 40.1% of subjects who received SD/SD. In COV003, all subjects received SD/SD, and only 8.0% received the two doses with an interval of ≥12 weeks.

Restricted to seronegative participants at baseline who received the SD/SD regimen with a follow-up ≥15 days post second dose, the estimated vaccine efficacy was 62.6% (95% CI (50.9, 71.5)) [DCO 7 Dec]. Restricted to seronegative participants at baseline who received the LD/SD regimen with follow-up ≥15 days post second dose the estimated vaccine efficacy was 90.1% (95% CI (65.84, 97.10)) [DCO 4 Nov].

Based on the above, the basis for pooling the LD/SD and SD/SD regimens set out in the CHMP scientific advice were not met (i.e. similar immunogenicity and efficacy across regimens), and the observed heterogeneity cannot allow to disentangle the different factors potentially affecting vaccine efficacy (e.g. dose interval, dose, age, attack rate) due to known and unknown confounders. Therefore, the SD/SD analysis set is considered to provide the more accurate estimate for recommending a posology. In addition, the vaccine

efficacy for the SD/SD set should be restricted to subjects who received the second dose within an interval from 4 to 12 weeks, as per agreed posology.

Efficacy for subjects who received SD/SD seronegative with a 4-12 week dose interval (i.e. 28 to 84 days) was 59.5% (95% CI: 45.8, 69.7), a result which was in line with that observed for the SD/SD independently of the time interval between doses [62.6% (95% CI: 50.9; 71.5)].

The vaccine efficacy in adults with comorbid conditions was consistent with the level of protection in the general study population [VE 58.3% [95% CI: 33.6; 73.9]; cases: 25 (1.2%) vs 60 (2.9%) for vaccine (N=2,068) and control (N=2,040) groups respectively]. Approximately 39% of participants in the primary efficacy population (LD/SD+SD/SD), as well as of the overall study population, had at least one comorbidity at baseline. Among those with comorbidities, the most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%).

Rate of prevention of severe COVID-19 could not be estimated since the number of cases were low. In seronegative participants at baseline in the SD/SD set and with follow-up ≥15 days after the second dose (4-12 weeks interval), there were 0 severe cases in the vaccine arm and 1 case in the control arm. With respect to hospitalisation there were 0 (0.0%; N=5258) cases of COVID 19 hospitalisation (WHO Severity grading ≥4) in participants who received two doses of the vaccine (SD/SD), ≥15 days post dose 2, 4-12 weeks interval) as compared to 8 (0.2%; N=5210) in the control group. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8032) cases of COVID 19 hospitalisation in participants who received the vaccine as compared to 14 (0.2%, N=8026) including one severe case (WHO Severity grading ≥6) and one fatality reported in the control group.

An immune response in terms of both the humoral response against S protein (binding antibodies) and SARS-CoV-2 virus (neutralization assays) and the cellular response have been shown in vaccinated subjects. In terms of binding antibodies, 100% of vaccinated subjects seroconverted (≥4-fold increase from baseline) after the second dose. The second dose is required to improve immunogenicity.

3.3. Uncertainties and limitations about favourable effects

The efficacy was based on a pooled analysis of two randomised controlled trials (COV002 and COV003). The conduct of studies was sub-optimal with regards to substantial changes to the protocol made after the start of studies, errors in dosing and an unplanned varying dose interval between 4 and 26 weeks. Adaptations to confirmatory trials introduced without proper planning reduce the confirmatory nature of the trial. The LD/SD regime showed a better humoral response and vaccine efficacy than the SD/SD regimen. It is not possible to elucidate the extent to which this effect can be attributed to the administered LD/SD dose, the longer interval between the 2 doses, chance, or differences in the distribution of other factors between the SD/SD and LD/SD populations.

The available data suggest that a longer interval between the first and second dose could be beneficial in terms of protection after the second dose. However, the independent effect of dose regimen and interval cannot be reliably estimated post-hoc based on the available data. Although immunogenicity data suggest that higher levels of neutralising antibodies are induced if the two doses are given at longer intervals, a differential effect of LD/SD cannot be completely excluded. Further, when vaccine efficacy estimates after two doses are calculated for individual intervals within the 4-12 week recommended interval (i.e. by 3 or 4 weeks periods) in the SD/SD set, it is difficult to conclude with certainty based on the available data that increased time intervals in the 4-12 weeks range induce an increase in vaccine efficacy.

Insight into vaccine efficacy between the first and second dose is particularly relevant considering the variable dosing interval proposed and the intended use within a pandemic, where there is a need to achieve protection as soon as possible. Several exploratory subgroup analyses were conducted in an attempt to estimate the protective efficacy during this interval. Protection starts from approximately 3 weeks after the first dose of vaccination.

The pooled VE in the time period starting 21 days after dose 1 until dose 2 (censored at 12 weeks post dose 1) in subjects who received SD/SD is estimated at 73.0% (95% CI: 48.9, 85.8). However, there is no consistency between the individual trials as in COV002 the VE for this interval is 44% (95% CI: -66.8, 81.3) whereas in trial COV003 it is 80% (95% CI: 55.3, 91.2). Relevantly, in COV003 the median interval between dose 1 and dose 2 is only 5 weeks, while in COV002 the median interval was 10 weeks. The UK study would therefore be best suited to study the maintenance of protection during the longer time interval up to 12 weeks, however, few cases were accrued as during this interval the attack rate was low. The Brazil study provided higher estimates of protection, but this is mostly driven by observations during the first few weeks after vaccination. A pooled estimate – driven mainly by observations from this shorter interval cannot be generalized to the full duration of 12 weeks between the first and second dose.

Additional uncertainties further hamper the interpretation of the pooled estimate such as the fact that the trial was not designed to estimate vaccine efficacy after first dose, and that similar or higher efficacy estimates are seen from 22 days post dose 1 vs. from 15 days post dose 2.

Therefore, the level of protection induced by one dose of COVID-19 Vaccine AstraZeneca over the full 12 weeks interval cannot be reliably estimated based on the available data.

In conclusion, the results show that the first SD dose provides at least some protective immunity starting 3 weeks after the first dose. Although the exact level of protection cannot be estimated, the first dose may offer sufficient protection up to 12 weeks. It is therefore important that a second dose is given after 4 and within 12 weeks after the first dose to achieve the protection suggested by the main study outcomes.

Efficacy could not be demonstrated in subjects older than 55 YOA due to the low number of COVID-19 cases in this age group. In the overall pooled efficacy set there are 8 cases in the AZD1222 group and 9 cases in the control group in subjects 56-65 years, and 2 and 6 cases in the vaccine and control group respectively in subjects older than 65 years of age. This is mostly due to the low number of subjects of this age who were recruited (13% of the pooled efficacy analysis set aged 65 years or older and 2.8% aged 75 or older), in addition to the short time of follow-up for this population – as they were enrolled after safety in adults was confirmed. This is considered a major limitation of the dataset since older adults are at high risk for complications upon SARS-CoV-2 infection.

However, based on the immunogenicity data available for this age group and on the experience with other vaccines, at least some protection is expected in this subgroup, although the exact level cannot presently be estimated. In order to obtain a metric on the vaccine efficacy in this subgroup, the interim and final results for study D8110C00001 (an ongoing phase 3 confirmatory trial that includes a substantial number of older adults) will be provided post-authorisation.

Although encouraging trends were observed, reliable efficacy estimates against severe COVID-19 and hospitalisation caused by COVID-19 could not be established due to the lack of a sufficient number of cases within the clinical studies. From the experience with other vaccines it is expected that prevention of severe COVID-19 will be achieved by preventing COVID-19 overall.

Data on vaccine efficacy is available for approximately 11 weeks of follow-up since dose 2. Therefore, the duration of protection is unknown. However long-term vaccine efficacy data will become available from post-authorisation studies.

No correlate of protection has been established.

Efficacy against asymptomatic infection could not be demonstrated (VE in SD/SD dataset: 7.66%, 95%CI -96.25, 56.55). As the observed number of cases was low, effect estimates are imprecise. Although the presence of viral RNA as collected via self-administered nasopharyngeal swabs may be evidence of infection, it does not provide any information of the infectivity of a person, i.e. his or her ability to transmit the virus to other persons. Insight into the impact of AZD1222 on transmission is likely to come from effectiveness studies conducted post-authorisation.

Available data are insufficient to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline. However, efficacy is anticipated in this group to the extent that natural immunity does not fully protected against re-infection, which is presently incompletely characterised.

There is no data on immunocompromised patients and limited data in pregnant and breast-feeding women. Further data in these subjects is planned to be collected post-authorisation.

Data are limited in subjects with severe and/or uncontrolled underlying disease.

There is no data in persons with autoimmune diseases since these subjects were excluded from the clinical trials.

The extent of cross-neutralisation of circulating and newly emerging strains of SARS-CoV-2 is unknown. More data will be generated post-authorisation. Further, a full characterisation of breakthrough cases within the studies will be informative to identify whether these are caused by variants escaping immunity elicited by the vaccine.

Concomitant administration of other vaccines has not been studied, which at this stage is acceptable. However, knowledge on concomitant administration of other frequently used vaccines such as, e.g. yearly influenza vaccines is considered valuable, and the applicant is requested to investigate this post-authorisation.

3.4. Unfavourable effects

The safety database includes over 12,000 subjects in the pooled safety dataset. Reactogenicity data was collected in a subset of 2,648 participants receiving Dose 1 SD for 7 days following any dose. Information on unsolicited adverse events was collected for 28 days after vaccination (any dose), information on adverse events of special interest and serious adverse events is collected for the entire study duration. The available number of days of follow up for SAEs and AESIs is currently approximately 100 days after the first dose and 55 days after the second dose of the vaccine respectively (DCO 04 November 2020).

Any Solicited local and systemic AEs were reported more frequently in AZD1222 than in the control group (86% and 71.7% of evaluated participants, within the first 7 days following any dose of AZD1222 or control treatment, respectively). The most frequently reported solicited local AEs after any dose SD of AZD1222 were tenderness (75.3% vs 54.2% in subjects who received MenACWY as control) and pain (54.2% vs 35.4% in control). Local reactions were self-limiting with a mean duration of 3.3 days following the first dose of AZD1222 group and 2.3 days following the second dose.

The most frequently reported solicited systemic AEs after any dose SD of AZD1222 were fatigue (62.3% vs 48.0% in subjects who received MenACWY) and headache (57.5% vs 42.4% in control); other frequently reported systemic solicited AEs were muscle pain (48.6%), and malaise (44.2%). Pyrexia was reported in 9.2% participants who received any dose of AZD1222 (vs 0.5% in subjects who received MenACWY).

Most of the systemic AEs following AZD1222 were mild or moderate and self-limiting with a mean duration of 2.8 days following the first dose and 2.7 days following the second dose. However, 9.3% of subjects experienced grade 3 systemic AEs, being malaise, chills and feverishness the most frequently grade 3 solicited systemic AE reported.

A single Grade 4 event was reported after the first dose in the AZD1222 group for fever (i.e., > 40°C).

Any unsolicited AEs were reported more frequently in the AZD1222 group than in the control group (meningococcal vaccine or saline) . Unsolicited AEs were largely consistent with AEs observed following vaccination, such as vaccination site pain, headache, malaise, fatigue and fever. A majority of them was mild to moderate in severity, showing a reduction of the percentages (related or not) after the second dose in both the study vaccine and the comparator. The most frequently unsolicited related AEs by SOC (Any Dose for Safety analysis Set) were general disorders and administration site conditions (23.4%), nervous system disorder (9.3%) and musculoskeletal and connective tissue disorders (2.7%) in AZD1222. The frequencies were higher in AZD1222 than in the control group (12.8%, 5.5%, 1.6%, respectively).

Most related AEs reported were grade 1, related AEs grades 2-4 were slightly more frequent in the AZD122 group. The overall incidence of AESIs was low: 0.8 % of participants in the AZD1222 group (95 cases) and 1.1 % in the control group (126 cases). The majority of the reported events were paraesthesia, hypoesthesia and muscular weakness, accounting for 57 of 95 AESIs in the AZD1222 and 76 of 126 cases in the control group.

Overall, the incidence of SAEs was low and similar in the AZD1222 and control groups (that includes both subjects receiving saline or a meningococcal vaccine). Fewer than 1% of participants reported a SAE overall (any dose). The most frequently reported SAEs by SOC in the AZD1222 and groups were Infections and Infestations (0.1% and 0.2% of participants respectively) and Injury, Poisoning and Procedure Related Complications (0.1% in both groups).

Only ≤0,1% participants reported a SAE considered treatment-related by the investigator, 2 in the AZD1222 group and 2 in the control group (pyrexia, myelitis transverse, autoimmune haemolytic anaemia and myelitis).

Other serious adverse events with a neuro-inflammatory aetiology have been observed in the safety database for which relatedness to the study treatment cannot be excluded at this stage (see section 3.5).

Further, there have been three other events with a potential neuro-inflammatory aetiology in ongoing studies which were not part of the submission for CMA: an event of Sensory neuropathy (D8110C00001 study), an event of Chronic Inflammatory Demyelinating Polyradiculopathy (D8110C00001 study), and a case of acute encephalopathy in the COVISHIELD study. This event is suspected to be a nutritional encephalopathy; however, an autoimmune aetiology has not been ruled out (see section 3.5).

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data is not yet available. Participants in the clinical trials will be followed until 364 days after any dose of AZD1222. The currently available number of days of follow up for SAEs and AESIs was approximately 100 days after the first dose and 55 days after the second dose of the vaccine respectively. Long-term safety is considered as missing information in the Safety specification in the RMP, and will be characterised as part of the continuation of the pivotal clinical trial, other trials and a PASS.

Slightly lower reactogenicity was observed with regard to incidence and severity in subjects who were seropositive for SARS-CoV-2 at baseline compared with subjects who were seronegative for SARs-CoV-2 at baseline. The proportion of seropositive subjects was much smaller (4.9%), when compared to the seronegative population receiving any dose of AZD1222 vaccine (95.1%), so this data is not definitive, but no safety issues were identified in seropositive subjects.

It is not clear whether vaccination is implicated in any of the events of a neuro-inflammatory nature observed also because events occurred in both the treated and controlled arms (myelitis, CIDP, facial spasm, encephalopathy and sensory neuropathy). These events had a varying clinical presentation, and do not point towards a clear and specific risk associated with the vaccine. Altogether the safety database is large, with over 12,000 subjects in the pooled analysis and approximately 15,000 subjects exposed in study D8110C00001. Therefore, although these events are rare, it is not impossible to observe these cases in a safety database of this size. Nonetheless, the occurrence of SAEs within this SOC shortly following vaccination with AZD1222 should not be dismissed and deserves close follow up because of the seriousness of the events. Neuro-inflammatory conditions should be carefully monitored, and regular updates are needed to inform of any new events in the SOC of Nervous System disorders or any serious or severe events with a neuro-inflammatory aetiology. Therefore, these have been identified as a potential important risk in the RMP with adequate surveillance measures.

Apart from the cases described above, for which aetiology is currently unknown, no autoimmune adverse events where identified as causally related to vaccination. Nonetheless, rare events of this nature cannot be excluded despite the large size of the available data set. Post-authorisation monitoring is important.

Safety data in participants with severe immunodeficiency, or participants with severe underlying disease (including autoimmune or inflammatory disorders) are lacking, as all these populations were excluded from the studies. The safety of AZD1222 in immunocompromised subjects will be evaluated post-authorisation.

Over a third of participants had comorbidity at baseline. There were no imbalances in the unsolicited AEs, SAEs and AESIs between the AZD1222 and control group for either comorbidity subgroup and between individual comorbidity subgroups.

Further, there is only very limited clinical experience in pregnant women, with 14 pregnant women in the safety database who were exposed to AZD1222. Data from non-clinical studies do not indicate any harm during pregnancy. In the absence of clinical data to confirm lack of risks, risks during pregnancy remain, albeit theoretical. Considering the ChAd vector is a non-replicating vector, and considering the small amount that is administered intramuscularly, it is deemed unlikely that this vaccine may pose a specific risk during pregnancy, apart from the risk that may be associated with a fever-reaction. Use of AZD1222 in pregnant and breast-feeding women will be investigated in the planned PASS.

The available data (non-clinical, clinical, neutralizing capacity of antibodies) do not raise a concern regarding vaccine-associated -enhanced disease for the time being. However, the possibility of enhanced disease

cannot be excluded with certainty. The RMP lists VAED as an important potential risk to be followed up post-authorisation.

3.6. Effects Table

Table 39: Effects Table for COVID 19 Vaccine AstraZeneca intended for active immunisation to prevent COVID-19 caused by SARS-CoV-2 (data cut-off: 4 November and 7 December 2020)

Effect	Endpoint	Unit	Vaccine	Control*	Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy overall (SD/SD+ LD/SD analysis set, any dose interval)	First COVID-19 (any severity) occurring 15 days after Dose 2 in individuals without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	66.45% (56.9, 73.9) 82	 240	Robust data with similar VE across different trials/Countries and subgroups such as subjects with comorbidities Vaccine group N=7485 Placebo N=7475	Pooled analysis of Studies COV002 and COV003 (DCO2, 07 December 2020)
Vaccine efficacy in the SD/SD analysis set (dose interval 4-12 weeks)	First COVID-19 (any severity) occurring 15 days after Dose 2 in individuals without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	59.5 (45.8, 69.7) 64	 154	Subgroup analysis supporting approved posology Vaccine group N=5258 Placebo N= 5210	
Vaccine efficacy against hospitalisation	First COVID-19 hospitalisation (WHO scale ≥4) occurring 15 days after Dose 2 in individuals without prior evidence of SARS-COV-2 infection First COVID-19 hospitalisation from 22 days after Dose 1	VE % (95% CI) COVID-19 cases COVID-19 cases	100% (42.6%, NE) 0 0	 8 14	Ad hoc analysis for the SD/SD Seronegative for Efficacy Analysis Set (dosing interval 4 to 12 weeks) Efficacy estimate uncertain due to limited number of cases One severe COVID-19 case reported in control (WHO scale ≥6)	

Effect	Endpoint	Unit	Vaccine	Control*	Uncertainties/ Strength of evidence	References
Vaccine efficacy in individuals aged >65 years	First COVID-19 (any severity) occurring 15 days after Dose 2 in individuals without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	67.02 (-63.97, 93.37) 2	 6	Subgroup analysis for the SDSD seronegative for efficacy analysis set, 4 to 12 weeks dosing interval Efficacy estimate uncertain due to limited number of cases/participants Vaccine N=621 Control N=617	

Unfavourable Effects**

Effect	Unit	Vaccine (post dose 2)	Control* (post dose 2)	Uncertainties/ Strength of evidence	References
Injection site pain	% of individuals reporting the ADR	54.2	36.7	Transient events, majority mild to moderate in severity median duration of follow-up 62 days post-dose 2 ADRs reported after dose 2 were milder and reported less frequently than after dose 1 ADRs generally milder and reported less frequently in older adults (≥65 years old)	Pooled data from COV001, COV002, COV003 and COV005 studies (Any dose for Safety Analysis Set) Control (N= 11,724) Vaccine (N=12,021)
Injection site tenderness		63.7	39.5		
Headache		52.6	48.5		
Fatigue		53.1	59.9		
Myalgia		44.0	36.7		
Arthralgia		26.4	19.7		
Malaise		44.2	32.1		
Nausea		21.9	19.3		
Chills		31.9	17.1		
Fever >38°C		7.9	2.9		
Feverishness		33.6	22.5		

Abbreviations: VE: vaccine efficacy; CI: confidence interval, DCO: data cut off; ADR: adverse drug reaction

Notes:

* control: MenACWY vaccine in all studies except for saline solution in study COV005

**only the most frequently reported adverse reactions are listed. For a full summary of all adverse reactions refer to the Summary of Product Information section 4.8.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, vaccine efficacy of two doses of 2.5×10^8 infectious units of AZD1222 administered with an interval of 4 to 12 weeks has been demonstrated for the prevention of symptomatic COVID-19 disease in adults 18 to 55 years of age, as well as an acceptable safety profile for subjects from 18 years of age and above based on the studies included in this MAA.

Due to the consistency in effect between studies as demonstrated after the second dose, and the reliable manner in which the primary endpoint was measured throughout the studies (as demonstrated by the similar proportions tested SARS-CoV-2 cases negative between study arms), it can be concluded that efficacy has been demonstrated. Based on a pooled analysis of two randomised controlled trials (COV002 and COV003), the primary endpoint results are considered sufficiently precise and provide a solid indication of protective efficacy of around 60% in non-elderly subjects.

This level of protection can be expected to translate into a relevant impact on the ongoing pandemic through preventing a substantial proportion of disease.

Whilst an optimal timing for the administration of the second dose within the 4 to 12-week interval cannot be determined based on the currently available data, the range of dose intervals as used in the studies has resulted in acceptable efficacy from 15 days after the second dose onwards.

Further, the exact level of protection between the two doses cannot be reliably estimated and although it is likely that there will be some level of protection starting from three weeks after the first dose, it is very important that the second dose is given.

No reliable efficacy estimate could be established against severe COVID-19 or hospitalisation; however, it is likely that severe disease will be prevented as a consequence of preventing symptomatic COVID-19. Further follow up is expected in post-authorisation effectiveness studies to confirm this.

Additionally, no effect was observed on asymptomatic infections with SARS-CoV-2 due to the low number of cases. Whilst it would be desirable to have insight into the potential impact of vaccination with AZD1222 on viral transmission, this cannot be concluded based on clinical trials data and will likely be further elucidated through effectiveness studies post-authorisation.

Efficacy could not be demonstrated in the groups 56 to 65 years of age, and in subjects 65 years of age and older due to the limited number of subjects enrolled in these age groups. However, taking into account the safety and immunogenicity profile, based on which efficacy is inferred, the benefit/risk balance can be considered positive for these age groups.

Efficacy has been shown in subjects with comorbidities defined as a BMI ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes.

There is considerable uncertainty regarding the duration of protection due to the short median follow up of approximately 11 weeks post second dose. In the current situation, these knowledge gaps are outweighed by urgent medical need, high COVID-19 disease burden, and lack of or limited availability of preventative and therapeutic remedies against COVID-19.

The observed safety profile is considered well characterised and acceptable based on short term data. ADRs are generally mild to moderate and are self-limited, although local tolerability and systemic ADRs overall indicate that this vaccine appears more reactogenic than many of the standard vaccines in use.

Long term safety has to be characterised further, and it is important to analyse the full year safety follow-up of the ongoing trials. The current dataset gives no indication of vaccine-enhanced disease, a potential risk that should be followed up as detailed in the RMP.

There are very limited data on use in pregnant women, but a protective effect is anticipated. Preliminary preclinical data are reassuring; therefore, noting that pregnancy as such is a risk factor for severe COVID19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis. Data in pregnancy will be generated post-authorisation. There are no data in breast-feeding women. Based on biological plausibility, no risk in breast-feeding is anticipated.

No participants with severe immunodeficiency were included in the studies. Such patients may not be protected as well as immunocompetent individuals by vaccination. However, no safety issues are anticipated, and the B/R balance in immunocompromised subjects is deemed positive, also in light of the underlying excess risk of COVID-19. Further data will be collected post-authorisation.

Also, subjects with severe underlying diseases were not included in the studies, and the safety of the vaccine in these groups will be followed up post-authorisation.

Regarding seropositive subjects, no safety issues have been observed in this population, and efficacy can be anticipated. Therefore the vaccine can be administered without performing previous SARS-CoV-2 serology testing.

Not all data are available for the process performance qualification, for the final demonstration of comparability to materials used in the clinical studies and to complete stability of the active substance and finished product. Despite these limitations in the quality data, the available data and the proposed specifications are considered scientifically justified and acceptable in the context of a CMA in an emergency situation.

3.7.2. Balance of benefits and risks

The available clinical data for AZD1222, including the induction of immune responses and the demonstrated vaccine efficacy, establish the benefits to prevent COVID-19 in immunized individuals 18 years of age and older. The lack of any serious safety concerns for subjects aged 18 years and above allows concluding on a positive benefit/risk balance in the proposed indication. Due to the inability to estimate the vaccine efficacy for subjects aged 56 and older, a warning is included in the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties could be addressed post-authorisation through specific obligations, including the continuation of the pivotal studies as long as possible, provision of additional data to confirm the B/R from other ongoing studies as well as post-approval effectiveness studies and safety surveillance.

3.8. Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of the vaccine.

The active substance and finished product are acceptable in relation to control of critical quality attributes and impurities.

Studies to demonstrate batch-to-batch consistency of the active substance and finished product in terms of process validation studies/process performance qualification studies (PPQ) have not been fully completed in the active substance and finished product commercial manufacturing sites. Nonetheless, sufficient data have been provided for full scale lots (including some PPQ lots) at the commercial sites and at other sites using the commercial process. Preliminary data suggestive of lack of homogeneity in one lot is being investigated and mitigation measures to introduce enhanced sampling to ensure batches are consistent have been put in place. These data lead to the conclusion that the risk of inconsistency in product quality is low.

Similarly, due to the speed of development in the pandemic scenario a comprehensive package to demonstrate comparability of these PPQ lots to clinical material has not yet been provided. However, the comparability data provided for the full-scale lots (including some PPQ lots) manufactured at each site do support a conclusion that the commercial product will be comparable to clinical material. The validation and comparability data will be completed using a concurrent validation strategy based on approved validation and comparability protocols with approved acceptance criteria. As a specific obligation the applicant will provide the completed process validation and comparability data for all of the commercial manufacturing sites.

The proposed specifications, as demonstrated by the submitted data, are suitable to control product quality. However, the lower shelf life limits for the infectivity specification are not fully confirmed and this could have potential impact on product potency. Despite this, sufficient clinical data have been provided to support the lower infectivity specification limit for authorisation and with this specification, a negative impact on product potency is considered unlikely. Due to the speed of development, real-time stability data for active substance and finished product are limited but data from clinical material are considered representative to support the respective AS and FP shelf-life. As a specific obligation the applicant will provide additional AS and AS stability data and will review the infectivity release and shelf life specifications as additional clinical data becomes available.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed in section 3.7.2.
- It is likely that the applicant will be able to provide comprehensive data.

Despite the limitations in the quality data relating to the fact that data are not yet completed for the process performance qualification, final demonstration of comparability to materials used in the clinical studies and stability of the active substance and finished product, the available data and the proposed specifications are considered scientifically justified and acceptable in the context of a CMA in an emergency situation.

In order to confirm the consistency of the active substance and finished product manufacturing process, the applicant will provide additional validation, comparability and stability data. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the applicant's plans and

documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between February 2021 and June 2022.

Furthermore, the applicant will continue the ongoing pivotal phase 3 randomised, control studies COV001, COV002, COV003 and COV005 to obtain 1-year long-term data and to ensure sufficient follow-up and provide the pooled analysis in order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca. Moreover, the applicant will continue the ongoing phase 3 randomised control study D8110C00001 in order to obtain a vaccine efficacy estimate for the elderly population, as this study includes higher numbers of this subpopulation with the primary analysis expected by 30 April 2021. The completion of these studies will lead to comprehensive date on the efficacy and safety of COVID-19 Vaccine AstraZeneca.

- Unmet medical needs will be addressed.

There is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Currently there are only two mRNA vaccines approved in the EU to prevent COVID-19 disease. Despite the recent granting of a conditional marketing authorisation for Comirnaty and COVID-19 Vaccine Moderna, there is still an urgent need to provide prophylactic options in the context of the pandemic across the EU.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The demonstrated efficacy and the satisfactory safety profile support the immediate availability of the product in the current emergency setting, notwithstanding the outlined uncertainties.

3.9. Conclusions

The overall B/R of COVID-19 Vaccine AstraZeneca is positive.

Eligibility to a conditional marketing authorisation as well as fulfilment of the requirements have been demonstrated in line with provisions of Article 14-a of Regulation (EC) No 726/2004.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of COVID-19 Vaccine AstraZeneca is favourable in the following indication:

"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 use of this vaccine should be in accordance with official recommendations".

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the consistency of the active substance and finished product manufacturing process, the applicant should provide additional validation and comparability data and, introduce enhanced testing.	December 2021 with interim monthly updates beginning February 2021

Description	Due date
In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.	June 2022 with interim monthly updates beginning February 2021
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should submit the final Clinical Study Reports for the randomised, controlled studies COV001, COV002, COV003 and COV005.	31 May 2022
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should provide the primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Primary analysis: 5 March 2021 Final pooled analysis: 31 May 2022
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	Primary analysis: 30 April 2021 Final CSR: 31 March 2024

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S) is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Annex I – List of Recommendations (RECs) and Legally binding measures (LEGs)

Area	Number	Description	Classification*	Due date
Quality	1	The applicant is requested to provide the results of the replication-competent adenovirus (RCA) testing of the master virus seed (MVS) phenotypic stability at passage 5 when available, as already committed, by February 2021.	REC	See description
Quality	2	It is recommended that the applicant removes the in-vivo adventitious agent testing from in process control from the bulk harvest (AS manufacturing process), as already committed, by March 2021.	REC	See description
Quality	3	The applicant is requested to review the AS and FP comparability ranges for future comparability exercises when more manufacturing experience is available as already committed by June 2021. The company has already committed to this, by June 2021.	REC	See description
Quality	4	The applicant is requested to update the AS process validation- Section S.2.5 of the dossier with completed reports, a description of the differences among the manufacturing sites and a listing of all lots included in process validation and corresponding lot release data, as already committed by June 2021. The applicant is also requested to review the acceptable ranges of the CPPs and the non-criticality of the NCPPs after the AS manufacturing process validation has been completed at three manufacturing sites by June 2021.	REC	See description
Quality	5	The applicant is requested to provide a table of process parameters and outputs and their validation acceptance criteria, including justification of differences between sites (for AS manufacture), as already committed by March 2021.	REC	See description
Quality	6	It is recommended that the applicant provides AS shipping qualification studies as already committed by June 2021.	REC	See description
Quality	7	It is recommended that the applicant submits the results of the method comparison study for host cell protein method used in the comparability study as already committed by March 2021.	REC	See description
Quality	8	It is recommended that the applicant performs an enhancement and inhibition study for the Endotoxin LAL test for three AS lots. The report of the study should be provided, as already committed by March 2021.	REC	See description
Quality	9	The applicant is requested to provide all method transfer or method validation reports by February 2021 (viral particle concentration, identity) or March 2021 (other transfer report/validation).	REC	See description
Quality	10	It is recommended that the applicant performs and provides a report of a study to demonstrate that microbial bioburden can be recovered from AS samples, as committed by March 2021.	REC	See description
Quality	11	It is recommended that study results of the method comparison between testing sites for infectivity, residual nuclease and host cell DNA are provided, as committed by March 2021.	REC	See description

Quality	12	The applicant should include the analytical results of hold time studies and, process intermediate hold time validation studies from all AS sites intended for EU commercialisation, as committed by May 2021.	REC	See description
Quality	13	The applicant should provide validation of tangential flow filtration membrane lifetime, active substance shipping qualification studies and validation of reprocessing, 0.2 µAS refiltration (all still in progress), as committed by May 2021.	REC	See description
Quality	14	The applicant is requested to validate and implement the transgene expression test for AS and FP testing in all testing sites, as committed by June 2021. Monthly status updates on method development, validation, and method transfer will be submitted beginning on 05 March 2021 and continuing until full transfer and implementation at all applicable testing sites is completed not later than June 2021	REC	See description
Quality	15	The applicant is requested to assess the combined impact of all holds on the cumulative decrease in infectivity during the AS hold times upon completion of the small-scale process hold intermediate study. The assessment should include a comparison of the cumulative fold decrease in infectivity based on the study data compared to target levels to assure adequate control of infectivity over the hold times, as committed by May 2021.	REC	See description
Quality	16	The applicant is requested to complete characterisation (all tests as detailed currently in the dossier for this purpose) for at least for one GMP AS batch manufactured using the commercial Process, as committed by May 2021.	REC	See description
Quality	17	The applicant is requested to review the AS specification when AS analysis data of 30 batches are available, as already committed, by September 2021.	REC	See description
Quality	18	The applicant is requested to submit a variation to extend the AS shelf life, supported by real time data.	REC	See description
Quality	19	The applicant is requested to evaluate the possibility of including transgene expression in the AS stability studies, as committed by June 2021.	REC	See description
Quality	20	It is recommended that the applicant submits the results of the FP formulation robustness studies when these are completed, as committed by May 2021.	REC	See description
Quality	21	It is recommended that the applicant performs in-use stability testing of an additional FP batch, which is towards the end of shelf-life, as committed by December 2021.	REC	See description
Quality	22	It is recommended that the applicant provides the test results of the simulated transportation stress exposure studies for the different FP configurations (vial presentations), as committed by June 2021.	REC	See description
Quality	23	Some FP validation studies are still on-going and the applicant has committed to provide the completed study reports by February 2021 as committed and results of the FP shipping qualification studies, by March 2021 as committed.	REC	See description

Quality	24	The applicant is requested to provide the results of the FP process hold studies, validation of labelling and secondary packaging at commercial scale when available, as committed by March 2021.	REC	See description
Quality	25	The applicant is requested to study whether it is possible to withdraw more than 8/10 doses for the FP presentation, as committed by February 2021.	REC	See description
Quality	26	The applicant should provide the results of the endotoxin product specific enhancement and inhibition study for three FP lots from two FP manufacturing sites and method suitability for the sterility method at each site, as committed by March 2021.	REC	See description
Quality	27	It is recommended that the applicant re-evaluates the appearance specification after 100 FP batches have been manufactured and tested, as committed by September 2021.	REC	See description
Quality	28	The applicant is requested to review the FP specification when more FP analysis data becomes available, as committed by September 2021.	REC	See description
Quality	29	The applicant is requested to provide the initial risk assessment on elemental impurities (ICH Q3B) by 05 March 2021, as committed by March 2021.	REC	See description
Quality	30	The applicant should evaluate the current testing strategy for the infectivity assay, as committed by April 2021.	REC	See description
Quality	31	The applicant is recommended to provide a report summarising the homogeneity testing of batches manufactured before implementation of the testing scheme in Specific Obligation 1f. It is recommended that this analysis includes testing performed on two samples per batch, taken at the beginning, middle and end of the filling. It is expected that a report is provided summarising batch results to date in Feb 2021.	REC	See description
Quality	32	It is recommended that the applicant updates the FP analytical procedure sections for compendial methods with unequivocal references to Ph. Eur. Methods as committed by February 2021.	REC	See description
Quality	33	It is recommended that the applicant performs a confirmatory photostability study in accordance to ICH Q1B, as committed by May 2021.	REC	See description
Quality	34	It is recommended that the applicant reports any results from the initiated FP leachable study that may lead to a safety concern, to EMA and the rapporteurs. The eCTD should be completed with the results of the completed study, as committee by January 2023.	REC	See description
Quality	35	It is recommended that for the AS PACMP, the summary table of process validation parameters and acceptance criteria is updated (if applicable) once all validation activities for the sites relevant for the Conditional Marketing Authorisation have been completed, as committed by May 2021.	REC	See description

Quality	36	For the root cause analysis (RCA) of the investigation into homogeneity, progress reports to be provided monthly from 18 February until resolution of the RCA investigation and any necessary corrective actions are agreed.	LEG	See description
Noncli nical	37	With reference to the NHP pharmacology study (Van Doremalen et al, 2020), the Applicant should provide a review of the relevant scientific literature and other available data to determine if the high level of viral RNA in the GI found only in vaccinated animals is an aberration or if there is a biologically plausible explanation. In such case, the clinical relevance of the finding should also be discussed.	REC	As soon as possible
Noncli nical	38	Regarding study 6284 and PRNT data after challenge, The Applicant is asked to explain the discrepancy in the CT scores on day 5 and 12 between appendix 10 and the corresponding tables in the report and module 2.6.2, and to confirm which scores are correct. Potential consequences on the vaccine-induced protection against lung pathology should be discussed.	REC	As soon as possible
Noncli nical	39	Limited assessments were made regarding the humoral and cellular immune response. Data on antibody subtypes, Th1/2 response, T cell subtyping and determination of neutralizing antibodies after vaccination and challenge was rather limited and, in some cases, completely absent. The Applicant should provide the complete results from study 20-01125 and summarize the main results to be included in the corresponding modules with an appropriate critical discussion.	REC	As soon as possible
Noncli nical	40	Some of the ferrets in study 20-01125 presented a reaction leading to death that was ascribed to the presence of BSA derived from the culture media used for virus growth. This can be a result of the pre-existence of anti-BSA antibodies derived from the required husbandry vaccination. A full report for these events should be provided.	REC	As soon as possible
Noncli nical	42	The Applicant should provide the final report for study 514559 (biodistribution in mice) as soon as available.	LEG	30 April 2021
Noncli nical	43	The final report for the DART study 490843 in mice should be provided as soon as available.	LEG	30 April 2021
Clinical	44	Provide data on cross-neutralisation for clinically relevant and emerging SARS-CoV-2 strains by testing sera from human clinical trial participants in functional in vitro assays.	REC	As soon as possible
Clinical	45	Provide clinical characterization and data on deep sequencing of virus from breakthrough COVID-19 cases evaluated in the phase 2 and/or 3 trials to identify any potential gap in protection against mutant strains.	REC	As soon as possible
Clinical	45	The Applicant has been asked to pre-specify how waning of vaccine efficacy will be studied post-authorisation if follow-up time accumulates, especially how the likely unblinding and crossover to the alternative arm will be accounted for.	REC	As soon as possible
Clinical	46	The Application should investigate the need for a booster dose and immunological correlates of protection.	REC	As soon as possible

Clinical	47	The Application should investigate the need for an immunological correlates of protection.	REC	As soon as possible
Clinical	48	The Ct values for the RT-PCR for subjects who were found to have asymptomatic SARS-CoV-2 infection should be submitted. Additionally, the applicant should comment if the viral load, in case of asymptomatic infection, was impacted by vaccination	REC	As soon as possible
Clinical	49	The applicant is requested to estimate in study COV002 a relative frequency of asymptomatic versus symptomatic infections in each study arm (acknowledging that observation-time would need to be equalized, and that symptomatic and asymptomatic infections are likely to be competing events).	REC	As soon as possible
Clinical	50	For the pseudoneutralization antibody assay, clarification was requested around specificity and cross-reactivity of the assay, as well as specific questions on the biological matrixes and limits of detection. Questions on the live neutralizing antibody assay centred around the number of clinical specimens that fell above and below the ULOQ and LLOQ, respectively.	REC	As soon as possible
Clinical	51	Additionally, data on the master virus used in the qualification and the robustness of the microneutralisation assay were posed to the applicant are requested.	REC	As soon as possible
Clinical	52	Further details on the size of the validation data set for the qualitative assay to assess nucleocapsid antibodies by electrochemiluminescent are requested.	REC	As soon as possible
Clinical	53	Clarification on the mechanism for qualifying the peptides used in the IFNγ ELISPot assay is requested to be provided).	REC	As soon as possible
Clinical	54	The applicant should discuss the reason for the difference in GMTs after the second dose between the Brazil and the South African studies, and whether this could be due to variability in testing between laboratories. The Applicant should also explain the difference in the size of the immunogenicity dataset between said studies.	REC	As soon as possible
Clinical	55	Due to the potential auto-immune aetiology in two SAEs events affecting the CNS, the applicant is requested to discuss whether there may be potential molecular mimicry between the viral vector and human tissue from the CNS. To this end, the applicant may perform a Basic Local Alignment Search Tool (BLAST) search.	REC	As soon as possible