Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report
Authorisation for Temporary Supply

COVID-19 Vaccine AstraZeneca, solution for injection in multidose container
COVID-19 Vaccine (ChAdOx1-S [recombinant])

Department of Health and Social Care (DHSC)
AstraZeneca AB

LAY SUMMARY

COVID-19 Vaccine AstraZeneca, solution for injection in multidose container
COVID-19 Vaccine (ChAdOx1-S [recombinant])

This is a summary of the Public Assessment Report (PAR) for COVID-19 Vaccine AstraZeneca, solution for injection in multidose container. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as COVID-19 Vaccine AstraZeneca in this lay summary for ease of reading.

For practical information about using COVID-19 Vaccine AstraZeneca, patients should read the Information for UK recipients on COVID-19 Vaccine AstraZeneca or contact their doctor or pharmacist.

What is COVID-19 Vaccine AstraZeneca and what is it used for?
COVID-19 Vaccine AstraZeneca is a vaccine indicated for active immunisation of individuals 18 years of age and older for the prevention of coronavirus disease 2019 (COVID-19).

How does COVID-19 Vaccine AstraZeneca work?
COVID-19 Vaccine AstraZeneca stimulates the body's natural defences (immune system) and causes the body to produce its own protection (antibodies) against the virus. None of the ingredients in this vaccine can cause COVID-19.

How is COVID-19 Vaccine AstraZeneca used?
The pharmaceutical form of this medicine is a solution for injection and the route of administration is intramuscular injection. COVID-19 Vaccine AstraZeneca will be given to you by an authorised practitioner as an intramuscular injection into the muscle at the top of the upper arm (deltoid muscle).

You will receive 2 injections of COVID-19 Vaccine AstraZeneca, each of 0.5ml. You will be told when you need to return for your second injection of COVID-19 Vaccine AstraZeneca. The second injection can be given between 4 and 12 weeks after the first injection.

For further information on how COVID-19 Vaccine AstraZeneca is used, refer to the Information for UK recipients on COVID-19 Vaccine AstraZeneca and Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This vaccine can only be obtained with a prescription.

If a person has any questions concerning the vaccine, they should ask the administering healthcare practitioner.

What benefits of COVID-19 Vaccine AstraZeneca have been shown in studies?
COVID-19 Vaccine AstraZeneca has been given to approximately 24,000 individuals aged 18 years or older in four ongoing clinical trials in the UK, Brazil and South-Africa. Most

were equally allocated to COVID 19 Vaccine AstraZeneca or a control (another vaccine not targeting SARS-CoV-2 or a placebo).

In a pre-specified preliminary analysis, those who received the vaccine had a reduction in the rate of COVID-19 illness compared to those who received the control (30 cases of COVID-19 illness in the vaccinated group compared to 101 cases in the control group). These results were observed two weeks or more after the second dose in study participants with no evidence of prior SARS-CoV-2 infection.

A similar benefit was observed in participants who had one or more other medical conditions that increase the risk of severe COVID-19 disease, such as obesity, cardiovascular disorder, respiratory disease or diabetes.

What are the possible side effects of COVID-19 Vaccine AstraZeneca?
The most common side effects with COVID-19 Vaccine AstraZeneca (which may affect more than 1 in 10 people) were tenderness, pain, warmth, redness, itching, swelling or bruising where the injection is given, generally feeling unwell, feeling tired (fatigue), chills or feeling feverish, headache, feeling sick (nausea), joint pain or muscle ache. In clinical studies, most side effects were mild to moderate in nature and resolved within a few days with some still present a week after vaccination

For the full list of all side effects reported with this medicine, see Section 4 of the Information for UK recipients on COVID-19 Vaccine AstraZeneca or the Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca available on the MHRA website.

Why was COVID-19 Vaccine AstraZeneca approved?
It was concluded that COVID-19 Vaccine AstraZeneca has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects observed with use of this product are considered to be similar to those seen for other vaccines. Therefore, the MHRA concluded that the benefits are greater than the risks and recommended that this medicine can be authorised for temporary supply during the COVID-19 pandemic.

What measures are being taken to ensure the safe and effective use of COVID-19 Vaccine AstraZeneca?
All new medicines approved require a Risk Management Plan (RMP) to ensure they are used as safely as possible. An RMP has been agreed for the use of COVID-19 Vaccine AstraZeneca in the UK. Based on this plan, safety information has been included in the Information for UK Healthcare Professionals and the Information for UK recipients, including the appropriate precautions to be followed by healthcare professionals and patients.

All side effects reported by patients/healthcare professionals are continuously monitored. Any new safety signals identified will be reviewed and, if necessary, appropriate regulatory action will be taken. The MHRA has also put in place an additional proactive safety monitoring plan for all COVID-19 vaccines to enable rapid analysis of safety information which is important during a pandemic.

Other information about COVID-19 Vaccine AstraZeneca
Authorisation for the temporary supply of COVID-19 Vaccine AstraZeneca was granted in the UK on 29 December 2020.

The full public assessment report for COVID-19 Vaccine AstraZeneca follows this summary.

This summary was last updated 31 December 2020.

TABLE OF CONTENTS

I INTRODUCTION

This report is based on the information provided by the company in a rolling data submission procedure and it covers the authorisation for temporary supply of COVID-19 Vaccine AstraZeneca. At the time of writing the company have provided sufficient information to make a decision on the vaccine but final reports for all studies have not yet been received: in addition, a reproductive toxicology study is ongoing.
Quality aspects of the vaccine are reviewed on a batch-specific basis.

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China and in January 2020, a novel coronavirus was discovered as the underlying cause. Infections by the virus, named SARS-CoV-2, and the resulting disease, COVID-19, have spread globally. On 11 March 2020, the WHO declared the COVID-19 outbreak to be a pandemic.

The number of COVID-19 cases in the UK now stands at more than 2 million and over 70,000 deaths have been attributed to the disease. The elderly and those with pre-existing medical conditions are at particular risk of severe disease and death from COVID-19. A new variant of SARS-CoV-2 has recently been identified which has a higher transmission rate than the other variants in circulation. Currently there is no evidence that this variant causes more severe disease or higher mortality. Vaccination is the most effective medical intervention to decrease risk and reduce spread of the SARS-CoV-2 virus.

The Department of Health and Social Care (DHSC) is leading the Government's deployment of vaccinations against COVID-19. In order to save lives, and to reduce the number of people who need hospital treatment due to COVID-19, the DHSC have sought to deploy a safe and effective vaccine as soon as possible. In a letter dated 24 November 2020, the DHSC requested authorisation, on a temporary basis, of its proposed supply of a vaccine manufactured by AstraZeneca AB named "COVID-19 Vaccine AstraZeneca", under Regulation 174 of the Human Medicines Regulations 2012, ("the Regulations"). Development of COVID-19 Vaccine AstraZeneca was initiated by the University of Oxford with subsequent transfer of development activities to AstraZeneca AB. In a subsequent letter dated 22 December 2020, and in light of knowledge of the new variant of SARS-CoV-2, the DHSC requested MHRA to consider the time interval between initial and booster doses of vaccine in which efficacy has been demonstrated, in order to provide operational flexibility and to enable a larger proportion of the population to receive a first dose in a shorter timeframe.

Following an extensive review of the quality, safety and efficacy data, COVID-19 Vaccine AstraZeneca has been authorised for temporary supply in the UK for the following indication: active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19). COVID-19 Vaccine AstraZeneca is a solution for injection stored at 2 – 8°C intended for intramuscular administration (IM). A single 4 mL vial contains 8 doses (each 0.5 mL) and a single 5 mL vial contains 10 doses (each 0.5 mL).

The SARS-CoV-2 virus uses proteins on its outer surface, called spike (S) proteins, to enter the cells of the body and cause disease. The active substance of COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector that codes for the S glycoprotein of SARS-CoV-2 (ChAdOx1-S [recombinant]). Following vaccine administration, this vector enters into the cells of the body and produces the S glycoprotein of SARS-CoV-2 which is then expressed on the surface of the cells. Expression of the spike protein induces neutralising antibodies and

T-cells to be raised against it. Should the body then become infected with SARS-CoV-2, the immune system will recognise the SARS-CoV-2 virus and attack it.

The authorisation is for specific batches of the vaccine, after confirmation that detailed conditions are met. The Conditions for Authorisation for COVID-19 Vaccine AstraZeneca are published on the MHRA website.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, analysis, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

This batch, and any future batches, of COVID-19 Vaccine AstraZeneca are subject to Qualified Person (QP) certification and batch evaluation by an independent control laboratory before the vaccine is released into the UK.

The COVID-19 Vaccine Benefit Risk Expert Working Group (Vaccine BR EWG) have met several times to review and discuss the quality, safety and efficacy aspects in relation to batches of COVID-19 Vaccine AstraZeneca.

The Vaccine BR EWG gave advice to the Commission of Human Medicines (CHM) on 29 September 2020, 14 October 2020, 10 November 2020, 7 December 2020, 10 December 2020, 17 December 2020, 22 December 2020, 24 December 2020, 29 December 2020 and 31 December 2020, regarding the requirements for authorisation for the temporary supply of COVID-19 Vaccine AstraZeneca. The requirements for quality, safety and efficacy were considered, taking into account the urgent public health need and risk to life, the pandemic situation and limited options for prevention and treatment of COVID-19. As well as data on quality, safety, efficacy and the timing of the second dose, specific conditions on the product were discussed to ensure adequate standards of quality and safety are met.

The CHM concluded that the proposed supply of COVID-19 Vaccine AstraZeneca for active immunisation to prevent coronavirus disease 2019 (COVID-19), in individuals 18 years of age and older, is recommended to be suitable for approval under Regulation 174 provided the company meets the Conditions for Authorisation for COVID-19 Vaccine AstraZeneca set out by the MHRA.

Authorisation for the temporary supply of COVID-19 Vaccine AstraZeneca was granted in the UK on 29 December 2020. This report covers data received and reviewed for this authorisation only. This authorisation is valid until expressly withdrawn by MHRA or upon issue of a marketing authorisation by MHRA.

Whilst an acceptable level of information has been received to provide assurance that appropriate standards of quality, safety and efficacy have been met for authorisation of specific batches for temporary supply under Regulation 174 of the Regulations, it should be noted that COVID-19 Vaccine AstraZeneca remains under review as MHRA continues to receive data from the company as it becomes available. This will include, for example, final study reports for all studies, long-term follow-up efficacy and safety data. Further information that is received by the MHRA will be reviewed as part of the ongoing

assessment for this product and updates will be made to this PAR to reflect that in due course.

II QUALITY ASPECTS

II.1 Introduction

This product is a colourless to slightly brown solution provided in a multidose vial of 2 different sizes: 10-dose drug product presentation (5 mL of vaccine) in a 6 mL vial or 10R vial, and an 8-dose drug product presentation (4 mL of vaccine) in a 5 mL vial.

One dose (0.5 mL) contains COVID-19 Vaccine (ChAdOx1-S recombinant) 5×10^{10} viral particles (vp), where ChAdOx1-S means the recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. The adenovirus is a non-enveloped virus.

The vaccine is produced in genetically modified human embryonic kidney (HEK) 293 cells. COVID-19 Vaccine AstraZeneca contains genetically modified organisms (GMOs).

In addition to ChAdOx1-S (recombinant) this product also contains the excipients L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injections.

The finished product is packaged in multidose vials of either: 5 ml of solution in a 10-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap (in packs of 10 vials); or 4 ml of solution in an 8-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with European Pharmacopoeia requirements.

II.2 ACTIVE SUBSTANCE

rINN: not assigned

The active substance is a clear to slightly opalescent solution.

Structure

The active substance, ChAdOx1-S (recombinant), is a recombinant, replication-deficient (E1 and E3 deleted) chimpanzee adenovirus that encodes the SARS-CoV-2 spike protein with a tissue plasminogen activator (tPA) leader sequence.

Adenoviruses are non-encapsulated, icosahedral particles (virions) between 80 and 100 nm in diameter, with prominent fibres protruding from the 12 vertices. The viral capsid is composed of three major proteins (fibre, hexon and penton) with four minor proteins (IIIa, VI, VIII and IX). The particles contain a single copy of the double-stranded DNA genome. The manufacturer has provided the DNA sequence of the 35,539 bp ChAdOx1-S (recombinant) genome.

The expression cassette for the SARS-CoV-2 spike protein fused to the tPA leader uses a modified human cytomegalovirus (CMV) promoter and a bovine growth hormone polyadenylation sequence.

The nucleotide sequence of the SARS-CoV-2 spike protein fused to the tPA leader encoded by ChAdOx1-S (recombinant) have been provided by the manufacturer.

General properties

Adenoviruses such as ChAdOx1-S (recombinant) are non-encapsulated, icosahedral particles (virions) between 80 and 100 nm in diameter, with prominent fibres protruding from the 12 vertices. The particles contain a single copy of the double-stranded DNA genome (contains a transgene to express the SARS-CoV02 virus spike [S] protein).

Viral genome size

The active substance, ChAdOx1-S (recombinant), has a genome size of 35,539 base pairs (bp).

ChAdOx1-S (recombinant) is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Manufacture of the drug substance

The manufacturer has provided details of the responsibilities of each facility involved in manufacture and testing including responsibilities performed by contract laboratories. A description of the manufacturing process and controls has been provided for each manufacturing site, including material inputs, critical and non-critical process parameters, and process outputs. The upstream process consists of working host cell bank vial thaw, inoculum expansion, infection with working virus seed and further expansion in the production bioreactor to generate ChAdOx1-S (recombinant). The downstream process consists of lysis of the production bioreactor cell culture, nuclease digestion of the host cell DNA, clarification and further processing through a series of purification/concentration steps to remove process-related impurities and then formulation with excipients and aseptic filtration.

The comparability between drug substance batches manufactured for the clinical program and drug substance batches representative of the commercial process has been evaluated. The data generated indicate consistency between the drug substance described for this application and that used in the clinical programme.

GMP certificates or a QP declaration have been provided for all relevant manufacturing sites, testing sites and QP release site. There are no GMP concerns.

Control of Materials

Raw materials are purchased from quality-approved suppliers according to approved procedures and are either compendial grade (i.e. defined in a Pharmacopoeia) or purchased in accordance with the vendor’s and/or manufacturer’s written specifications. No materials of human origin were used in the manufacturing process for COVID-19 Vaccine AstraZeneca other than the host cells, which are derived from the HEK293 human embryonic kidney cell line. Materials of animal origin used in pre-GMP virus seed development, GMP cell banking, virus seed banking and the manufacturing process have been adequately described. Information, certificates of origin and TSE certificates of suitability have been provided.

Satisfactory descriptions have been provided for all starting materials. Detailed descriptions are given for the development of the ChAdOx1 adenoviral vector, development of the recombinant spike protein gene, construction of the intermediate ChAdOx1 nCoV-19 BAC plasmid, and generation of the host cell line as well as the generation of the viral isolate and preparation of the research virus seed (RVS).

Details of the master host cell bank and working host cell bank have been provided as well as details of the master virus seeds (MVSs), working virus seeds (WVSs) and control cell cultures. Testing of the cell banks is in line with ICH Q5A (R1) and ICH Q5D. The cell banks were tested for identity, safety, and purity, and all test results met the acceptance criteria.

Tests include sterility, mycoplasma, adventitious and endogenous viruses and cell line species identification. A test for replication competent adenovirus (RCA) is conducted on every AZD1222 MVS and on every drug substance at the bulk harvest step to confirm the absence of replication competent adenovirus.

Controls of Critical Steps and Intermediates
Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. The microbial controls (in-process bioburden and endotoxin measurements) used to demonstrate microbial control of the manufacturing process for drug substance are described and found acceptable.

Process validation
Drug substance process validation studies are not yet complete, however, the general validation plans described appear acceptable. Full validation study results must be provided once available.

Characterisation
Appropriate proof-of-structure data have been supplied for the active substance.

Impurities
All potential known product-related impurities have been identified and characterised. The process-related impurities are divided into three categories: biologically-derived macromolecules, small molecules and synthetic macromolecules. These have been adequately evaluated and described.

Control of drug substance
An appropriate release specification is provided for the active substance. The manufacturer has provided adequate justification for these limits, based on efficacy and safety considerations, and/or well-established limits for other medicines (where this is appropriate). It is agreed that due to the relatively limited manufacturing experience to date the proposed specifications can be accepted at this time, by taking into account the efficacy and safety justifications. The specifications will be revisited and revised if appropriate after a suitable number of commercial batches have been prepared.

Validation of analytical procedure
Validation of the analytical methods used for the control of the drug substance are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses
Batch release results for all batches used in the clinical trials, along with site of manufacture, have been provided and show that all batches conformed to the specifications in force at time of manufacture.

Batch release data for the commercially manufactured drug substance lots that have been provided to date are all within specification and no major trends are apparent between the different manufacturing facilities.

All batch release results are provided and confirmed to be within specification before approval of each batch under Regulation 174.

Justification of specification
Acceptance criteria for stability and lot release testing are established within limits that ensure the safety and efficacy of the product and allow for reliable manufacturing and adequate shelf life needed for continued product supply. Some specifications are further justified based on manufacturing experience with other adenoviral products and/or compliance with regulations, guidance, and compendial monographs.

Reference Standard
The reference standard used for routine drug substance and drug product lot release and stability testing has been described. The reference standard is placed on stability. Preparation and qualification of the reference standard has been provided and is adequate.

Container Closure System
Suitable specifications have been provided for all packaging used. The two primary container closure systems for the drug substance have been described and are suitable for the intended use. Stability testing has shown the primary containers to be compatible with the drug substance. Long-term storage of the drug substance in the primary containers has been provided and is adequate.
The primary packaging has been shown to comply with the quality standards of the Ph.Eur.

Stability
The stability data provided are sufficient to support the proposed shelf-life of 6 months for the drug substance. The company has committed to continue the stability studies.

II.3 DRUG PRODUCT

COVID-19 Vaccine AstraZeneca is a sterile liquid dosage form intended as a multiple-dose vial for administration by intramuscular injection. The drug product is supplied in presentations containing either 8 doses or 10 doses per vial. COVID-19 Vaccine AstraZeneca is manufactured with clear and colourless vials, closed with elastomeric stoppers, and sealed with aluminium overseals. The drug product vials are packaged 10 vials in a carton.

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided. The sterile drug product dosage form was developed to ensure COVID-19 Vaccine AstraZeneca stability and to meet clinical dose level needs by intramuscular administration. The formulation composition was developed based on experience with adenoviruses.

All excipients, including water for injection (WFI) comply with the specifications of the Ph. Eur. None of the excipients are of animal or human origin, nor are any novel. The excipients are well established for pharmaceutical products.

This product consists of genetically modified organisms (GMO).

Manufacture of the drug product

A description of the manufacturing method has been provided. Drug product manufacturing consists of thawing, dilution, mixing sterile filtration, aseptic filling, visual inspection and labelling. The finished drug product is stored at 2-8°C.
The development of the clinical manufacturing processes have been adequately described. Comparability studies demonstrate that drug product from each process is comparable and conform to pre-defined comparability criteria.

A satisfactory batch formula has been provided for the manufacture of the product for presentations with 8 doses/vial, 5 mL vial size, 10 doses/vial, 6 mL vial size, and 10 doses/vial, 10R vial size.

An appropriate account of the manufacturing process has been provided for each drug product manufacturer. The manufacturing process has been adequately described and the manufacturing process controls in place are acceptable.

Controls of critical steps and intermediates

Adequate information on critical process parameters and in-process controls has been provided. Control of critical process steps for the manufacture of COVID-19 Vaccine AstraZeneca is described through critical process parameters, in-process controls, and in-process hold time.

Process validation

Drug product process validation studies are not yet complete, however, the general validation plans described appear acceptable. Full validation study results must be provided once available.

Control of excipients

All excipients are of compendial grade and none of the excipients are of human or animal origin. As the drug product excipients are tested according to compendial methods, no validation of the analytical procedures is required to be submitted for review.

Control of drug product

The finished product specification is satisfactory. The manufacturer has provided adequate justification for these limits, based on efficacy and safety considerations, and/or well-established limits for other medicines (where this is appropriate). It is agreed that due to the relatively limited manufacturing experience to date the proposed specifications can be accepted at this time by taking into account the efficacy/safety justifications. The specifications will be revisited and revised if appropriate after a suitable number of commercial batches have been prepared.

Analytical procedures

Validation of the analytical methods used for the control of the drug product are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses

Batch release results for all batches used in the clinical trials, along with site of manufacture, have been provided and show that all batches conformed to the specifications in force at time of manufacture.

Batch release data for the commercially manufactured drug product lots that have been provided to date are all within specification.

All batch release results are provided and confirmed to be within specification before approval of each batch under Regulation 174.

Independent Batch testing
Independent batch testing provides additional assurance of quality before a batch is made available to the market. Independent batch testing is a function that is undertaken by an Official Medicines Control Laboratory (OMCL) and, under Regulation 174A, the UK National Institute for Biological Standards and Control (NIBSC) is responsible for this function.

Independent batch testing is product-specific: it requires specific materials and documentation from the manufacturer and comprises laboratory-based testing and review of the manufacturer's test data. If all tests meet the product specifications a certificate of compliance is issued by the OMCL. NIBSC has developed the capability and capacity to undertake the independent batch tests for this product.

Characterisation of impurities
There are no new process related drug product impurities in addition to those described for the drug substance.

Justification of specifications
Acceptance criteria for stability and lot release testing are established within limits that ensure the safety and efficacy of the product, ensure consistent manufacturing and allow an adequate shelf life for continued product supply. Some specifications are further justified based on manufacturing experience with other adenoviral products and/or compliance with regulations, guidance, and compendial monographs.

Reference standards or materials
The reference standard used for the drug substance and the drug product are the same. This is acceptable as both drug substance and drug product have the same composition.

Container closure system
The container closure system has been well described and complies with the relevant quality standards of the Ph.Eur.

Stability
Finished product stability studies include batches of the finished product stored in the packaging proposed for marketing. The manufacturer has provided all stability data available to date. Based on the results, a shelf-life of 6 months at 2°C to 8°C for the unopened multidose vials is recommended.

The product should be stored in the original package in order to protect from light. During use, vials can be handled in room light conditions. It should not be frozen.

Since the vaccine does not contain a preservative, once the stopper has first been punctured, the vial should be used within 6 hours. After the first dose is withdrawn, the vaccine should be stored between 2°C to 25°C and used as soon as practically possible. After 6 hours, any unused vaccine left in the vial should be discarded.

Suitable post approval stability commitments have been provided to continue stability testing on batches of COVID-19 Vaccine AstraZeneca. The manufacturer has committed to provide these data to the MHRA on an on-going basis as it becomes available.

Handling and disposal
Distribution during deployment should be controlled at 2-8°C throughout its shelf life of 6 months.

Further packing down (splitting of packs) of lots to aid deployment, can occur at 2-8°C within its shelf life. This can also be implemented at 'room temperature' (less than 25°C), if completed within 2 hours, immediately prior to final pre-use distribution (at 2-8°C). GMP controls are required to ensure there is no detrimental impact to quality, safety or efficacy of the lots by this processing.

After first use, the vials should be marked with the date and time.

Disposal should take account of the fact that COVID-19 Vaccine AstraZeneca contains a genetically modified organism (GMO). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant.

II.4 Regulation 174

Authorisation for temporary supply of COVID-19 Vaccine AstraZeneca under this Regulation 174 has been given following review of batch specific data by MHRA.

Independent batch release by the National Institute for Biological Standards and Control (NIBSC) is performed on all batches to be supplied to the UK.

The quality data currently available for COVID-19 Vaccine AstraZeneca can be accepted as sufficient with specific conditions in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174 of the Human Medicine Regulations.

III NON-CLINICAL ASPECTS

III.1 Introduction

In vivo animal safety testing with the vaccine has been conducted and it was well tolerated with no adverse findings. At the time of writing, the only remaining data expected, that are in compliance with Good Laboratory Practice (GLP) are from a reproductive toxicity study in mice. This will be reported in 2021. The primary pharmacology data reviewed do use COVID-19 Vaccine AstraZeneca.

The following non-clinical information was reviewed for this application.

Primary Pharmacology

Graham, S. P. et al. Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19. *npj Vaccines.* **5**, 69 (2020)

Study INT-ChAdOx1 nCov19-POT-002 – To determine potency of the CBF manufacturing batch of COVID-19 Vaccine AstraZeneca in mice

Study 20-01125 - Assessment of efficacy of SARSCoV-2 vaccine candidates in the ferret model
Study 6285 – Efficacy of ChAdOx1 nCoV-19 against coronavirus infection in ferrets
van Doremalen, N. et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature*. **586**, 578-582 (2020)
Study 6284 – Efficacy of ChAdOx1 nCoV-19 against coronavirus in rhesus macaques

Safety Pharmacology
Study 617078-1158zm – Safety pharmacology study to assess potential effects on vital systems (cardiovascular, respiratory) of AZD1222 in male mice given a single intramuscular dose of AZD1222 (GLP)

Pharmacokinetics
Study uno0009/MAB-001 – AdCh63ME-TRAP tissue distribution study by intra-dermal administration to mice (GLP)
Study uno0014/RMBBioDIST-001- AdCh63 MSP-1 and MVA MSP-1 tissue distribution study by intra- muscular administration to mice (in-life phase conducted to GLP)
Study 514559 (protocol, study ongoing) – AZD1222 (ChAdOx1-nCovd-19): A single dose intramuscular vaccine biodistribution study in the mouse (GLP)
Study 0841mv38-001 (protocol, study ongoing) – ChAdOx-1 HBV and MVA-HBV biodistribution study in BALB/c mice with shedding assessment (GLP)

Toxicology
Study 513351 - AZD1222 (ChAdOx1-nCovd-19): A 6 week intermittent dosing intramuscular vaccine toxicity study in the mouse with a 4 week recovery (GLP)
Study QS18dl – ChAdOx1 Chik Vaccine or ChAdOx1 MERS: toxicity study by intramuscular administration to mice (GLP)
Study uno0013 - Mouse toxicity AdCh63 MSP-1 and MVA MSP-1 or a combination of AdCh63 ME-TRAP and MVA METRAP (GLP)
Study XMM0003 - ChAdOx1 NP+M1 and MVA NP+M1: toxicity study by intramuscular administration to mice (GLP)
Study 490838 - ChAdOx1-nCovd19: A preliminary intramuscular injection vaccine development and reproductive study in female CD-1 mice (GLP)
Study 490843 (ongoing) - AZD1222 (ChAdOx1 -nCovd19): An intramuscular vaccine development and reproductive study in female CD-1 mice (GLP)

Studies that were carried out in accordance with Good Laboratory Practice (GLP) are indicated above. There are no concerns in relation to GLP. In the study titles above COVID-19 Vaccine AstraZeneca is sometimes referred to as AZD1222.

III.2 Pharmacology
Immunogenicity studies were conducted in animal models responsive to COVID-19 Vaccine AstraZeneca in order to evaluate the immunological properties of this COVID-19 vaccine candidate to support first in human (FIH) clinical trials. COVID-19 Vaccine AstraZeneca has been shown to be immunogenic in BALB/c, CD-1 mice, ferrets, non-human primate (NHP) and pig models.

The studies summarised below included evaluation of humoral, cellular and functional immune responses. It is noted that the number of animals in groups was limited in some studies.

In the immunogenicity study, published by Graham et al, 2020, 'prime-boost' vaccinated inbred (BALB/c) and outbred (CD1) mice (9-10 weeks of age) were immunised by intramuscular (IM) injection of 10^8 infectious units (IU) of COVID-19 Vaccine AstraZeneca on 0 and 28 days post-vaccination, whereas, 'prime-only' mice received a single dose of the vaccine on day 28. Results showed a significant increase in antibody titre on prime-boosting in inbred mice when compared to primed-only mice but there was no boosting response seen in outbred mice. In both mouse strains the cellular response was primarily driven by CD8 +ve T cells. The absence of a booster response in outbred mice may have been due to the effect of a single dose being near to the maximal response. Mice showed Th1-like CD4+ and CD8+ve T cell responses. Both antibody- and T cell responses are thought likely to contribute to controlling infection. This study also investigated the immunogenicity of one or two doses of COVID-19 Vaccine AstraZeneca in pigs. Responses seen in pigs may be more representative of the likely human response. Pigs showed a booster response in serum antibody and showed Th1-like CD4+ and CD8+ve T-cell responses which are thought likely to contribute to controlling infection. In pigs, titres after a single dose of vaccine were similar to those in asymptomatic humans, whereas those after boosting were comparable to those in patients who recovered from COVID-19 disease.

Study 20-01125 evaluated the immunogenicity and protective activity of COVID-19 Vaccine AstraZeneca on challenge with SARS CoV-2. Ferrets can be infected with SARS-CoV-2 after its intranasal application, with virus shedding from the upper respiratory tract occurring for at least 9 days post exposure; however, they do not show signs of ill health. In this study no ferrets in either the vaccinated or control groups developed any signs of disease, indicating that the virus is not pathogenic in ferrets. Nevertheless, antiviral activity of the vaccine can be shown in this species. Data were presented on immunological analyses of ferret immune cell populations, cytokine profiles and proportions of IFN-γ producing cells following immunisation and subsequent challenge with SARS-CoV-2. Ferrets given a single intramuscular injection of COVID-19 Vaccine AstraZeneca developed neutralising antibodies, boosted by challenge with SARS-CoV-2. Ferrets given COVID-19 Vaccine AstraZeneca showed a faster reduction to undetectable limits of SARS CoV-2 virus in nasal samples than did ferrets not given COVID-19 Vaccine AstraZeneca.

Study 6285 assessed the immunogenicity of COVID-19 Vaccine AstraZeneca and its protective activity against SARS CoV-2 challenge in ferrets. A vector control group were given ChAdOx-1 GFP in which the gene insert for the viral spike protein was replaced by that for Green Fluorescent Protein (GFP) and a further group were assigned as unvaccinated controls. Twelve ferrets were vaccinated with COVID-19 Vaccine AstraZeneca, six with a prime only regime and six with a prime and boost doses, 28 days apart. Eight ferrets also received viral particles of ChAdOx1-GFP, four prime only and four prime boost. Six further ferrets were immunised with formalin-inactivated SARS CoV-2. Ferrets were challenged with SARS-CoV-2 via the intranasal route at 4 weeks after their last dose of vaccine (2 weeks for those given formalin-inactivated SARS CoV-2). The challenge was done on two separate days giving a cohort (a) that were all dosed on one day and cohort (b) that were all dosed on a different day. Overall, COVID-19 Vaccine AstraZeneca appeared to offer protection in this challenge model. Dosing was well tolerated and induced neutralising antibodies with booster dosing increasing neutralising antibody titres significantly although this enhancement did not appear to be sustained for much longer than a week. There was a good correlation between neutralising antibody titre with antibody binding to spike protein, suggesting that binding to spike protein is contributing to the neutralising activity of serum from vaccines. After viral challenge, vaccinated ferrets showed reduced challenge viral RNA in the upper respiratory tract and this was cleared earlier compared to controls. These results were mirrored by tissue

PCR results, which showed that in the upper respiratory tissues there was less detectable viral RNA in vaccinated ferrets. Lung histopathology in vaccinated ferrets appeared to be reduced, one-week post-challenge compared to controls but a deterioration was seen in vaccinated ferrets and the difference in lung histopathology between groups at two weeks post-challenge was negligible. The vaccine appeared to delay the appearance of lung pathology.

A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated enhanced respiratory disease (ERD) (van Doremalen *et al* 2020). This study showed that COVID-19 Vaccine AstraZeneca reduced clinical disease score in monkeys and prevented damage to the lungs upon challenge to the upper and lower respiratory tract with SARS-CoV-2 virus; a prime-boost regimen induced humoral immune responses. COVID-19 Vaccine AstraZeneca reduced viral load in the lungs, reducing virus replication in the lower respiratory tract. Despite this, there was no reduction in viral shedding from the nose with either prime-only or prime-boost regimens. These data support an interpretation that COVID-19 Vaccine AstraZeneca may not prevent infection nor transmission of SARS-CoV-2, but it may reduce illness. The immune responses were not skewed towards a Th2-type and there was no suggestion of disease aggravation following COVID-19 Vaccine AstraZeneca.

Study 6284 was done to test potential activity of COVID-19 Vaccine AstraZeneca to protect rhesus monkeys from a challenge with SARS-CoV-2 virus. In this study 3 male and 3 female monkeys were vaccinated once with COVID-19 Vaccine AstraZeneca and 3 male and 3 female monkeys with phosphate buffered saline, by intramuscular injection. Monkeys were challenged with SARS-CoV-2 virus four weeks later and killed on days 7 or 13 or 14 after viral challenge. COVID-19 Vaccine AstraZeneca induced neutralising antibodies and had an effect to reduce the magnitude of weight loss or temperature increase caused by SARS CoV-2 challenge. The vaccine appears to prime the immune system to release activated monocytes and T helper cells within the early days following SARS CoV-2 challenge and vaccinated monkeys appeared to have increased antigen-specific T cells following challenge. Vaccination offered some protection against disease as shown on a CT scan 5 days after challenge, this had abated by day 12. Lung lesion severity appeared to be reduced in most vaccinated monkeys at 1 or 2 weeks after the viral challenge and there was a reduction in viral RNA in the lung and bronchoalveolar lavage fluid in most vaccinated monkeys. There was, however, little evidence of reduction in viral RNA in the upper respiratory tract and at day 7 post-challenge, there appeared to be an increase in viral RNA in the large intestine of vaccinated monkeys. In summary, COVID-19 Vaccine AstraZeneca did offer a level of protection in this challenge experiment and did not appear to cause vaccine-enhanced disease.

Study 617078 was a safety pharmacology study designed to assess the potential effects of COVID-19 Vaccine AstraZeneca on the vital systems (cardiovascular, respiratory) in male mice given a single intramuscular dose of COVID-19 Vaccine AstraZeneca. Administration of COVID-19 Vaccine AstraZeneca resulted in a statistically significant decrease in respiratory rate and increase in inspiration and expiration time throughout the whole 4-hour recording period. These statistically significant differences were considered to be a consequence of the variability in pre-dose data and that the profile of these respiratory parameters appeared similar across all recording days and therefore these respiratory changes were considered not to be associated with COVID-19 Vaccine AstraZeneca. Dosing with COVID-19 Vaccine AstraZeneca did not result in changes in any of the other parameters monitored in this study: there were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters.

In summary, neither ferrets nor monkeys developed clinically evident disease after SARS CoV-2 and this places limitations on the ability to show that vaccination reduced disease. However, small group sizes contribute to the difficulty.

In the studies in ferrets and monkeys, evaluations were made of the safety profile of the vaccine. These evaluations confirmed changes at injection sites in the injected muscle and reactions consistent with a minor local inflammatory effect. These changes attributed to COVID-19 Vaccine AstraZeneca suggest that it is likely to be tolerable as an intramuscular injection and to have effects consistent with an immunogen.

There was, however, a finding of hepatitis in ferrets. In the literature, vaccination against SARS (not SARS CoV-2 note) was reported to enhance hepatitis in ferrets (Weingartl H *et al* 2004 J Virol 78(22) 12672-12676) but the vaccine used in that study was a modified vaccinia virus Ankara based vaccine, containing the gene for the SARS viral spike protein: neither of these characteristics offer insight as to whether COVID-19 Vaccine AstraZeneca might induce hepatitis. General toxicity studies are reported from mice as reviewed in this assessment report below. Further comment and a conclusion on potential liver toxicity is given there.

There is a theoretical concern of vaccine-associated disease enhancement, where use of COVID-19 Vaccine AstraZeneca might put vaccinated individuals at risk of worse disease if they later encounter SARS CoV-2. The study in rhesus monkeys, however, did not identify evidence of concern of this effect following vaccination with COVID-19 Vaccine AstraZeneca.

The safety pharmacology investigations did not identify a concern for use of COVID-19 Vaccine AstraZeneca. Although there was an apparent effect of the vaccine, examination of the trace above shows that at baseline, the respiratory rate was already lower in those mice who later were dosed with COVID-19 Vaccine AstraZeneca: all the groups showed a reduction and that in those given COVID-19 Vaccine AstraZeneca seemed no greater than in the other groups.

III.3 Pharmacokinetics

The vaccine is intended to be given as an intramuscular injection. Two biodistribution studies were performed which suggest that, after injection, the virus does not replicate, or persist and it is not detectable except at the injection site.

Absorption

No absorption studies were performed with COVID-19 Vaccine AstraZeneca since the route of administration is intramuscular (IM).

Distribution

COVID-19 Vaccine AstraZeneca has been manufactured so that it is unable to replicate in cells. Therefore, after infecting a cell, there is expected to be no further spread of the virus.

Study uno0009/MAB-001 was a biodistribution study performed in compliance with Good Laboratory Practice, in which mice were injected with AdCh63METRAP virus. The study was carried out to determine the distribution of infectious adenovirus particles in mouse organs one week after a single intradermal dose in the ear. Two mice were also analysed immediately after injection. The results suggest that the virus is lost from the injection site over time and a lack of replication in tested mouse tissues. AdCh63METRAP was only

detected at the injection site, and not in any other organs. These results are consistent with the injection of a non-replicating virus. However, of note when interpreting these data, the study report notes that immediately after injection, AdCh63METRAP will begin to enter cells and is no longer available to infect the HEK 293 cells used in the assay.

Study uno0014/RMBBioDIST-001 evaluated tissue distribution following a single IM dose in mice each of different viruses, AdCh63 MSP-1 and MVA MSP-1. Results for the virus MVA MSP-1, an attenuated pox virus, are not described here as they are not relevant for what is expected with COVID-19 Vaccine AstraZeneca. Results showed AdCh63-MSP1 was detected at the injection sites on the day of dosing but not at 24 hours or 7 days later. No AdCh63-MSP1 was detected in any internal organ. Comparing between these two studies into distribution, the report comments that the route of administration appears to affect the persistence of infectious virus at the injection site as by the intramuscular route, virus was only detectable at the injection site immediately after injection. These results are consistent with the injection of a replication deficient virus for AdCh63-MSP1.

Study 0841mv38-001 was a biodistribution and shedding study using the ChAdOx1 vector with a hepatitis B virus (HBV) insert after IM injection on days 1 and 28 in mice. Distribution to some samples of all tissues was noted on day 2 and day 29. The highest levels (copies/mg sample) were noted at the site of administration (skeletal muscle), ranging from 3 x 10^8 to 9.97 x 10^9 copies/mg sample. In the majority of samples of other tissues taken on day 56, the levels were below the level of quantification, indicating elimination. Low levels were noted in 1 sample (of 6) for each of heart and liver, 1 of 3 for ovary and testes, and 3 of 6 lymph node samples at this timepoint. This study does not contain assessment of CNS, relevant peripheral nerves or bone marrow and it does not include analysis at shorter time points compared to the already available studies and no description of the validation of method analysis. This platform study will be superseded by Study 514559, designed to explore the distribution of COVID-19 Vaccine AstraZeneca after a single intramuscular injection in male and female mice. A draft report is expected February 2021.

Metabolism
No metabolism studies were performed.

Excretion
No excretion studies were performed.

In summary, COVID-19 Vaccine AstraZeneca is an unadjuvanted vaccine containing a replication-incompetent virus. As such, the virus should not spread at all far from the site of its administration and this profile was confirmed for the viruses tested where it was identified at the injection site and its draining lymph node. These results are considered suitable to stand in place of a dedicated study with COVID-19 Vaccine AstraZeneca as the same results would be expected. It is agreed that it is reasonable to omit an *in vivo* study in mice, as animal use for this purpose is not expected to provide any additional useful information on COVID-19 Vaccine AstraZeneca.

The active principle is not the immunogen but is the induced immune response. The time course of immune response induced is of interest: this has been characterised to a sufficient extent in the pharmacodynamic studies described above.

Absorption, metabolism and excretion studies are not required for vaccines: this position is in line with relevant regulatory guidance (WHO guidelines on nonclinical evaluation of vaccines, 2005).

The pharmacokinetic data presented are acceptable.

III.4 Toxicology

Single dose toxicity

No single dose toxicity studies have been performed with COVID-19 Vaccine AstraZeneca. This is acceptable and in line with relevant guidelines (WHO 2005; WHO 2014).

Repeat dose toxicity

Study 513351 was a 6-week intermittent dosing intramuscular vaccine toxicity study in the mouse with a 4-week recovery. The objective of this study was to determine the potential toxicity of COVID-19 Vaccine AstraZeneca (total viral particle dose of $3.7x10^{10}$) when given by IM injection intermittently (on days 1, 22 and 43) to mice, with a 28 day recovery period to evaluate the potential reversibility of any findings. In addition, the immunogenicity was evaluated. Scheduled necropsies were conducted either at the end of the 6-week treatment period (day 45) or at the end of the 28 day recovery period.

Administration of COVID-19 Vaccine AstraZeneca to CD-1 mice (total viral particle dose of 3.7×10^{10}) by intramuscular injection on 3 occasions (once every 3 weeks) over a 43 day period was well tolerated, with a transiently higher body temperature in males, decreases in monocytes in males and females (consistent with the expected pharmacology of COVID-19 Vaccine AstraZeneca) and increase in globulin and decrease in albumin and albumin/globulin ratio, consistent with an acute phase response, observed. In all animals dosed with COVID-19 Vaccine AstraZeneca, antibodies against the S-glycoprotein were raised and maintained throughout the dosing and recovery periods in all animals. In COVID-19 Vaccine AstraZeneca animals, higher spleen weights were observed but with no correlating macroscopic or microscopic changes. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with COVID-19 Vaccine AstraZeneca which were consistent with the anticipated findings after intra-muscular injection of an immunogenic vaccine.

Study QS18dl was performed to investigate the potential toxicity of ChAdOx1 Chik or ChAdOx1 MERS in inbred (Balb/c) mice, aged 8 weeks old and weighing ~20g, when given as an IM injection on two occasions, 14 days apart. Following a 13 day observation period the mice were killed and subject to post mortem examinations. The doses of ChAdOx-1 Chik and of ChAdOx-1 MERS were each 1×10^{10} viral particles, in 25 or 35 µl per injection. Each mouse was injected twice on each dosing day, in the left and the right hindlimb. These vaccines were in development to prevent chikungunya (a viral infection spread by mosquito bites) and middle eastern respiratory syndrome (MERS, camel flu; a coronavirus that causes a respiratory illness) and can be considered to be similar to COVID-19 Vaccine AstraZeneca. Results showed that each of these vaccines were well tolerated and was not associated with any adverse effects. All the effects described are expected as responses to injection of a vaccine, reflecting immune stimulation and/or the response to introduction of the injecting needle into muscle tissue. The changes in the lumbar lymph node reflect that this is the lymph node local to the injection site in the hindlimb. The slight increases in glucose, potassium and phosphorus and decreases in triglycerides and liver weight may not be direct

effects of vaccination and there was a reduction in body weight gain, but the magnitude of these effects was small, and these changes were not considered adverse.

Study un0013 evaluated the potential toxicity of AdCh63 MSP-1 and MVA MSP-1 or a combination of AdCh63 ME-TRAP and MVA ME-TRAP in inbred (Balb/c) mice when given as an IM injection on two occasions, 14 days apart, followed by a 13 day observation period, when mice were killed and subject to post mortem examinations. These vaccines were developed to prevent malaria. Results showed that there were no signs of toxicity in response to these vaccines: the changes noted are consistent with effects of an immune response to a vaccine, including a mild inflammatory reaction at intramuscular injection sites.

Study xmm0003 was performed with vaccine containing the ChAdOx1 construct but with a gene insert other than from SARS-CoV-2. Ten male and 10 female BALB/c mice were given one IM injection with vaccine ChAdOx1 NP+M1 then 14 days later were given a booster dose with a different vaccine, MVA NP+M1. Control mice were given saline on days 1 and 15. Mice were followed to day 13 after their second dose and then killed for post mortem analyses. The antigen in this vaccine was derived from influenza. The results demonstrated changes considered to be consistent with an immune response to vaccination, reflecting in the lymph nodes, likely, B cell proliferation, and of increased white blood cells with some local inflammation at the injection site.

Genotoxicity
No genotoxicity studies were performed.

Carcinogenicity
No carcinogenicity studies were performed. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005).

Reproductive and developmental toxicity
An evaluation of the impact of COVID-19 Vaccine AstraZeneca on embryo-fetal development was completed in a dose-range study (Study 490838). The main GLP embryo-fetal development study, Study 490843, is ongoing with an audited draft report due at the end of January 2021.

Prenatal and postnatal development
In Study 490838, control (group 1) or COVID-19 Vaccine AstraZeneca (group 3) was administered via the IM route to groups of outbred (CD-1) female mice on day 1 (13 days prior to pairing for mating to a non-dosed male) and again on gestation day (GD) 6 at 2.59 x 10^{10} per occasion (embryofetal development phase). In further mice, control (group 2) or COVID-19 Vaccine AstraZeneca (group 4) was administered via the IM route on GD 6 and GD 15 at 2.59 x 10^{10} per occasion (littering phase). Mice were killed either on day 17 (groups 1 and 3) or followed to day 14 post birth (groups 2 and 4). The dose used was either 0 (controls) or 2.59 x 10^{10} viral particles per dose, considered as a maximum feasible dose. For a 40g mouse, the dose represents an excess over humans of ~906.5 fold. A dose of 1.7x10^{10} virus particles in mice has been previously shown to induce an appropriate immune response. Results showed that anti-S glycoprotein antibody responses were raised in dams following administration of COVID-19 Vaccine AstraZeneca and these were maintained through the gestational and lactation periods. Seropositivity of fetuses and pups was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively. There were no COVID-19 Vaccine AstraZeneca -related effects seen for dams in-life

including at the injection site, for female reproduction, fetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no COVID-19 Vaccine AstraZeneca -related fetal visceral or skeletal findings.

Prenatal and postnatal development, including maternal function
See above.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
See above: no studies have been done in which juvenile animals were dosed directly.

Local tolerance
No such studies have been done. This was evaluated in general toxicity studies which is preferred to the conduct of separate studies to evaluate local tolerance.

Other toxicity studies
No such studies have been done.

Toxicity conclusions
The vaccine is to be provided as two doses (each 0.5 mL) given intramuscularly. One dose (0.5 mL) contains COVID-19 Vaccine (ChAdOx1-S* recombinant) 5 x 10^{10} viral particles (vp). * Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein.

Adenoviruses are double-stranded DNA viruses naturally present in the environment: some can cause mild illness. They have the capacity to infect mammalian cells independent of the cell cycle stage and so can infect post-mitotic cells and they can produce large amounts of progeny. However, removal of genes responsible for adenoviral replication eliminates this and the degree of pathogenicity should be reduced.

Mice were used in all toxicity studies and were selected as they show a reliable immune response to ChAdOx-1 vaccines and this was confirmed for COVID-19 Vaccine AstraZeneca. The choice of mouse for safety studies is accepted. A single species is acceptable; both males and females were evaluated.

The nature of toxicity was similar across these different studies: there were minor inflammatory reactions at the injection site and lymphoid organs showed an expected response to vaccination. Of note, the usual study design is to give one more dose to animals than is intended in humans. The general toxicity study with COVID-19 Vaccine AstraZeneca met this expectation. Given that the toxicity seen was minimal and the dose of vaccine used was in large excess of that to be used in humans, the general toxicity data presented suffice to support human use.

There was no indication of liver toxicity in mice and at necropsy livers appeared normal. It is possible that mice recovered from liver changes before the assessments of liver function and post mortem evaluations were made but this seems unlikely. Based on the biodistribution data presented, COVID-19 Vaccine AstraZeneca is not expected to reach the liver. Although identified in ferrets this was not seen in monkeys: overall, the vaccine seems to pose no special risk of liver toxicity.

The study reports did not indicate any changes of relevance to the brain and peripheral nervous system and there are no statements to the effect of any adverse or unusual behaviour in vaccinated mice.

Concerning the potential for induction of antibody-dependent disease enhancement, whereby use of the vaccine might put vaccinees at risk of worse disease, this risk is not well characterised. It is not clear at present even if this can be assessed appropriately in studies in animals. The general toxicity studies do not give any insights on this as the study designs do not include exposure to virus.

The mouse may not be the best choice of species for the evaluation of potential reproductive toxicity as the exposure to the organs of the fetus during their development to antibody induced by the vaccine probably did not occur. Nevertheless, international guidelines indicate that mice are an acceptable species for testing potential reproductive toxicity and no indication of harm was identified. Further information from the company will be supplied.

Considering potential use in women who are breastfeeding, the preliminary study does not give sufficient evidence of lack of risk and therefore a final recommendation on use in pregnant or lactating women cannot be made at this time. The ongoing GLP-compliant study should provide more information once it is completed. The information provided to healthcare professionals states that COVID-19 Vaccine AstraZeneca should only be considered in pregnancy when the potential benefits outweigh any potential risks for the mother and fetus.

The conclusion of this assessment is that COVID-19 Vaccine AstraZeneca could be supported for use in humans to prevent COVID-19. Further information is awaited to define the recommendation on use in women who are or may be pregnant or who are breastfeeding.

III.5 Ecotoxicity/Environmental Risk Assessment

It is agreed that, in accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, due to their nature, vaccines are unlikely to result in a significant risk to the environment. Therefore, an environmental risk assessment is not provided in this application. This is acceptable. This vaccine contains a genetically modified organism (GMO). However, consequences of release and persistence of the GMO in the environment are regarded as negligible.

III.6 Discussion on the non-clinical aspects

The non-clinical data currently available for COVID-19 Vaccine AstraZeneca can be accepted as sufficient with specific mitigations in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174.

IV CLINICAL ASPECTS

IV.1 Introduction

The immunogenicity, efficacy and safety data supporting this authorisation for temporary supply have been generated by four studies, presented below. COVID-19 Vaccine AstraZeneca is referred to as AZD1222 in this clinical review.

Table 1: Overview of AZD1222 studies

	COV001	COV002	COV003	COV005
Abbreviated Title	A phase I/II study to determine efficacy, safety and immunogenicity in healthy adult volunteers	A phase 2/3 study to determine efficacy, safety and immunogenicity; safety and immune-genicity sub-studies: • healthy children aged 5 to 12 years, inclusive • HIV+ adults aged 18 - 55 years	A Randomized, Controlled, Phase III Study to Determine Safety, Efficacy, and Immunogenicity	An adaptive phase I/II randomized placebo-controlled trial to determine safety, immunogenicity and efficacy in subjects without HIV; and safety and immunogenicity in subjects with HIV.
Region	United Kingdom	United Kingdom	Brazil	South Africa
Control	MenACWY (D1&2)	MenACWY (D1&2)	D1 MenACWY D2 Placebo (0.9% saline solution)	D1&2:Placebo: Normal saline (0.9% NaCl)
Age (years)	18-55	≥ 18	≥ 18	≥ 18-65
Paracetamol use	Prophylactic for a portion of participants	Prophylactic for a portion of participants	Prophylactic for all	As clinically needed
Primary endpoint	Virologically-confirmed (PCR+) symptomatic cases of COVID-19	Virologically-confirmed (PCR+) symptomatic cases of COVID-19	Virologically-confirmed (PCR+) symptomatic cases of COVID-19	PCT+ COVID-19 cases > 14 days after booster dose in participants COVID-19 naïve at the time of randomization and who received 2 doses of test product
No subjects **Planned/completed** **In the safety set**	 1122/1077 1067	 12390 10663	 10300 10002	 2070 2013

All studies have completed enrolment of their respective efficacy cohorts and are in the follow-up phase, with the exception of the paediatric group in COV002.

All studies were originally planned to investigate a single dose regimen but were amended in July 2020 to investigate a two-dose regimen in view of early immunogenicity results. The booster was planned to be given at the earliest possible time (in principle, 28 days after the prime dose), but due to logistical constraints, this interval was very variable.

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No pharmacokinetic data have been submitted for this application and none were required.

IV.3 Clinical immunogenicity

Bioanalytical assays
The qualification or validation reports for each bioanalytical assay have been provided. These include the neutralising assays (pseudoneutralisation and live neutralisation), binding anti-spike and anti-RBD antibody assays, ELISpot assay, and intracellular cytokine staining assay. Overall, the methods were considered acceptable and fit for purpose.

Study COV001
Initial data described hereafter were published in Lancet 2020; 396: 467–78 (Folegatti PM et al); Nat Med. 2020 (Ewer K et al). Overall, 88 healthy adults aged 18–55 years were randomly assigned to receive ChAdOx1 nCoV-19 (AZD1222) at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. Blood samples were drawn at days 3, 7, 14, 28, and 56 after vaccination. Ten participants assigned to a non-randomised group received a two-dose regimen, with the booster vaccine administered 28 days after the

first dose.

A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunisation augmenting neutralising antibody titres. After the booster dose, the levels of binding and neutralising antibodies were comparable to those of a panel of convalescent serum samples.

Anti-spike IgG responses at the peak of the response after vaccination (day 28) showed a polarized IgG1 response, consistent with naturally acquired antibodies against SARS-CoV-2, as well as an IgG3 response in most vaccinees. A mixed IgG1 and IgG3 response, with low levels of IgG2 and little detectable IgG4 is consistent with induction of Th1-type human IgG subclasses (IgG1 and IgG3).

Flow cytometry with intracellular cytokine staining (ICS) of peripheral blood mononuclear cells (PBMCs) stimulated with peptides spanning the S1 and S2 subunits of SARS-CoV-2 spike protein demonstrated antigen-specific cytokine secretion from CD4+, and to a slightly lesser extent CD8+, peaking 14 days after the vaccine dose. CD4+ responses were heavily biased toward secretion of Th1 cytokines (IFN-γ and IL-2) rather than Th2 (IL-5 and IL-13).

Based on this finding, it was decided to further investigate a prime-boost regimen of two doses of 5×10^{10} viral particles (20 subjects) or one dose of 5×10^{10} viral particles followed by one half dose (2.5×10^{10} viral particles) administered 8 weeks apart. These data were published in Nat Med 2020 (Barrett et al).

They confirmed that a second vaccine dose enhances both the titre and the functionality of the antibody response measured 28 days after the booster dose. Fc-mediated anti-spike antibody effector functions, which may have a role in the protection against COVID-19, were in the same range or higher than those measured in sera from convalescent patients. A booster dose of vaccine induced stronger antibody responses than a dose-sparing half dose boost, although the magnitude of T cell responses did not increase with either boost dose.

Study COV002 – Phase II part

These data were published in Lancet 2020 Nov 18:S0140-6736(20)32466-1 (Ramasamy MN et al). The study aimed at evaluating the impact of age on antibody and T cell responses to the vaccine. Three different age groups of subjects, 18-55, 56-69, and ≥ 70 years, respectively, received two doses of vaccine, 4-6 weeks apart. After a change in manufacturer, it was found that the first dose received by these subjects contained about half the intended number of viral particles; for the second dose, it was decided to administer the same lower dose and to recruit three other similar age groups that would receive two doses of the intended amount (5×10^{10}) of viral particles.

The median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts, and likewise, the neutralising antibody titres. The antibody response was generally comparable after the first dose and at its peak, 14 days after the booster dose, but tended to be slightly lower with the lower dose regimen compared to the standard dose regimen at day 56. T-cell responses peaked at day 14 after a single standard dose and did not increase significantly after the boost vaccination, with no trend according to dose or age.

In this study, the antibody response to the viral vector was also investigated. Anti-ChAdOx1 neutralising titres increased in all groups to similar levels but were not increased further after

a boost dose of vaccine at day 28. A weak negative correlation was found between anti-ChAdOx1 levels before the booster dose and the anti-spike IgG response to the booster dose.

Pooled analysis (COV001, -002, -003, -005)
The immune response to vaccination was assessed 28 days after the first and second doses in a subset of the trial subjects. Subgroup analyses were conducted by baseline serostatus (positive/negative), by age (18-64/ ≥ 65 years), by country (UK/Brazil/South Africa), and comorbidity (yes/no). A proportion of vaccines received a lower priming dose and the standard booster dose (LDSD) while the majority received two standard doses (SDSD). The results were presented overall (SDSD + LDSD) and in the two subsets (LDSD and SDSD).

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. 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 for seronegative participants.

For seronegative participants at baseline, an increase in S-binding antibodies was observed at 28 days after the first dose with a notable further increase at 28 days following the second dose. Of note, baseline seropositive participants also had increased S-binding responses after the first dose, but in contrast to the baseline seronegative group, antibody levels were not further increased by the second dose, which is consistent with an 'immune plateau' noted with other vaccines.

Geometric mean titres (GMT) for S-binding antibodies in the SDSD subgroup were numerically higher after the first dose compared with the GMT for the LDSD subgroup. Following the second dose, GMT further increased for both regimens, with an apparent higher GMT for the LDSD regimen. Similar results were observed for the other antibody assays.

Table 2: SARS-CoV-2 S-binding antibody levels by serostatus at baseline

			SDSD + LDSD		**SDSD**	**LDSD**
Subgroup	**Timepoint**	**Statistic**	**AZD1222**	**Control**	**AZD1222**	**AZD1222**
SEROSTATUS		N	1655	1197	1356	299
Seronegative	Post Dose 1	n / N_{sub}	885 / 1617	704 / 1166	817 / 1320	68 / 297
		GMT	**8156.07**	**56.85**	**8386.46**	**5836.18**
		(95% CI)	(7563.3, 8795.3)	(51.6, 62.6)	(7758.6, 9065.1)	(4340.4, 7847.4)
	Post Dose 2	n / N_{sub}	886 / 1617	705 / 1166	819 / 1320	67 / 297
		GMT	**30206.20**	**62.70**	**29034.74**	**48986.76**
		(95% CI)	(28271.0, 32273.9)	(56.3, 69.8)	(27118.2, 31086.7)	(38483.3, 62357.0)
Seropositive	Post Dose 1	n / N_{sub}	29 / 38	28 / 31	28 / 36	1 / 2
		GMT	**178522.42**	**7303.99**	**175120.84**	**305936.00**
		(95% CI)	(123872.3, 257283.1)	(3307.9, 16127.4)	(120096.9, 255354.8)	(NE, NE)
	Post Dose 2	n / N_{sub}	29 / 38	25 / 31	28 / 36	1 / 2
		GMT	**114488.67**	**8296.39**	**112978.13**	**166062.00**
		(95% CI)	(74664.2, 175554.8)	(4233.6, 16258.1)	(72553.8, 175925.4)	(NE, NE)

In the SDSD group, after starting from similar immune responses to the first dose there is a clear trend that longer dose intervals are associated with higher responses induced by the

second dose. The same pattern is reflected in the nAb responses. When comparing SDSD and LDSD groups with the same dose interval, the immune response after the second dose is similar. Given that the median dose interval in the LDSD group was 12 weeks compared with 5 weeks in the SDSD group in Brazil and 10 weeks in the SDSD group in the UK, these data suggest that the higher levels of immunogenicity engendered in the LDSD group are influenced more by interval than by dose level.

Table 3: SARS-CoV-2 S-binding antibody levels by dose level and interval (seronegative at baseline)

		SDSD				**LDSD**			
		AZD1222				**AZD1222**			
Visit Window	**Statistic**	**< 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	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

High seroconversion rates by S-binding antibodies were observed in older adults (≥65 years) after the first SD (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second SD (100.0% [N=111, 95% CI: 96.7; NE]). The GMT for S-binding antibodies were lower in adults ≥ 65 years of age than in younger adults after both the first dose and second dose. Similarly, nAb (pseudoneutralisation) GMTs were lower in the older adults. These data differ from those of Phase II in that 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 lower titres observed after the second dose.

Table 4: SARS-CoV-2 nAbs Levels (by Pseudoneutralisation Assay) by Age (seronegative at baseline)

			LDSD + SDSD		SDSD	LDSD
Subgroup	**Timepoint**	**Statistic**	**AZD1222**	**Control**	**AZD1222**	**AZD1222**
Age 18-64	Post Dose 1	n / N_{sub}	645 / 1373	522 / 994	500 / 1104	145 / 269
		GMT	**58.124**	**20.374**	**59.026**	**55.120**
		(95% CI)	(52.69, 64.12)	(19.99, 20.76)	(52.87, 65.90)	(44.35, 68.51)
	Post Dose 2	n / N_{sub}	651 / 1373	501 / 994	497 / 1104	154 / 269
		GMT	**181.790**	**21.487**	**173.708**	**210.528**
		(95% CI)	(166.36, 198.66)	(20.67, 22.33)	(156.52, 192.78)	(178.31, 248.57)
Age ≥65	Post Dose 1	n / N_{sub}	75 / 244	77 / 172	75 / 216	-
		GMT	**37.103**	**21.105**	**37.103**	**-**
		(95% CI)	(29.26, 47.05)	(18.96, 23.49)	(29.26, 47.05)	-
	Post Dose 2	n / N_{sub}	52 / 244	54 / 172	52 / 216	-
		GMT	**109.212**	**21.066**	**109.212**	**-**
		(95% CI)	(77.58, 153.73)	(18.98, 23.38)	(77.58, 153.73)	-

IV.4 Clinical efficacy

A pooled efficacy analysis, justified by the similar design of the four COV studies, has been conducted to support the use of AZD1222 to immunise adult subjects against COVID-19.

Methods

Study participants

Healthy adults, with no history of laboratory confirmed COVID-19 were enrolled in the studies. The main other exclusion criteria were subjects with immunodeficiencies or on chronic immunosuppressant therapy; subjects with history of angioedema or anaphylaxis; subjects with severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed); pregnancy, lactation or intention to become pregnant during the study (continuous effective contraception was required during the course of the study). Seasonal influenza and pneumococcal vaccinations were allowed with an interval of least 7 days before/after the study vaccine in some studies (otherwise 30 days).

Statistical analysis

The primary endpoint was the incidence of SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥ 15 days after the second vaccine dose. COVID-19 cases were PCR-confirmed with at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia, and confirmed by an adjudication committee.

The statistical analysis of vaccine efficacy (VE) used a Poisson regression model with robust variance to estimate the relative risk (RR) of the incidence of cases in the AZD1222 and control groups. The model contained the terms of study code, treatment group, and age group at randomisation (18-55 years, 56-69 years, and ≥ 70 years). The logarithm of the period at

risk for primary endpoint was used as an offset variable in the model to adjust for participants having different follow-up times during which the events occur.

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, was calculated as VE = 1- relative risk. The VE, and its corresponding 2-sided (1-α) % confidence interval (CI), was estimated from the model.

One interim analysis and a primary analysis were planned. 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. The analyses were to be triggered based on counts of COVID-19 cases that occurred ≥ 15 days after the second dose in participants who were randomised between SDSD and control. The interim analysis was triggered when at least 53 COVID-19 cases fulfilling the criteria above had occurred. The primary analysis would have been triggered when 105 COVID-19 cases had occurred. While the analyses were triggered by the number of cases in participants who received SDSD, cases in participants who received LDSD were also to be included for the analysis of the primary endpoint. This was estimated to provide an additional 10 and 20 cases at the interim and primary analysis respectively. A gamma alpha-spending function was used to control the overall Type 1 error at 5%.

The combined analysis was to be considered positive if the alpha adjusted confidence interval at either analysis had a lower bound > 20%. With assumptions of a true VE of 60% a total of 125 cases provides 96% power to achieve the pre-specified success criterion. Under the same assumption this number of events gives 83% power to achieve a confidence interval lower bound > 30%.

The main secondary endpoints included severe COVID-19, defined as ≥ grade 6 in the WHO clinical progression scale, hospitalisation, and asymptomatic SARS-CoV-2 infection, defined as PCR-confirmed SARS-CoV-2 infection and no symptom record.

The primary analysis was based on the SDSD + LDSD Seronegative for Efficacy Analysis Set, i.e., randomised participants who had received LDSD or SDSD, were seronegative at baseline, and had follow up data ≥ 15 days after the second dose.

Results

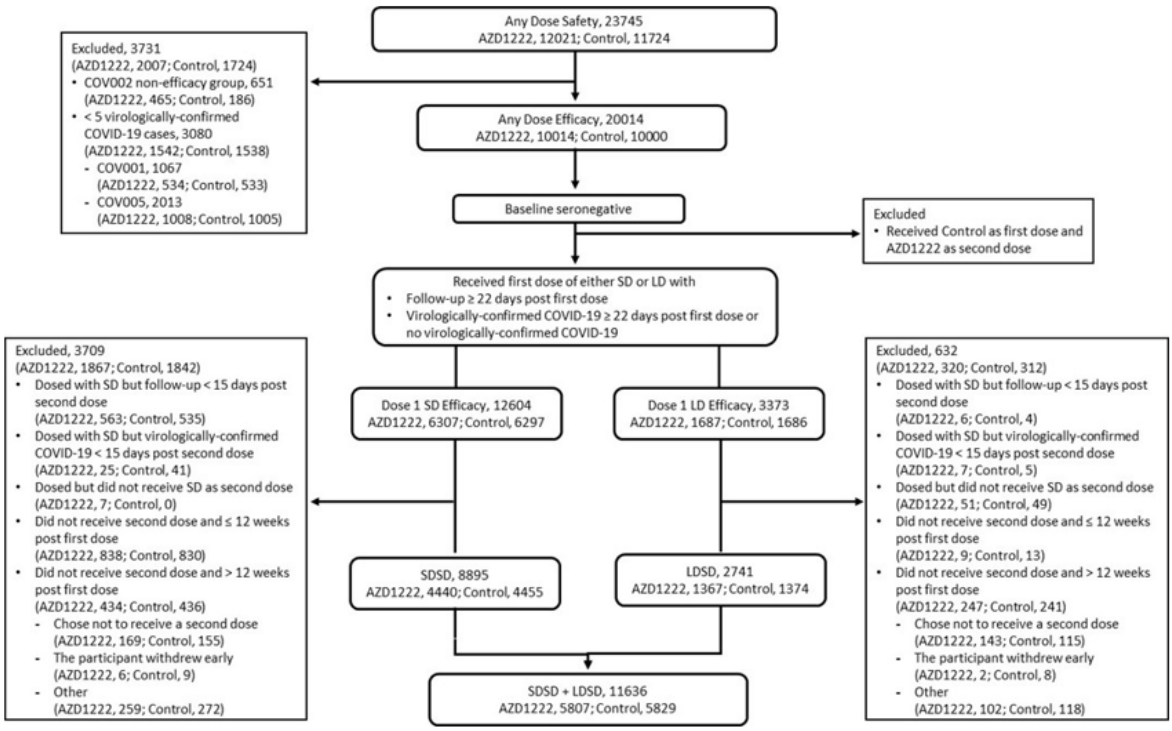
An interim analysis was conducted with a data cut-off date of 04 November 2020. Studies COV001 and COV005 were excluded as they had fewer than 5 cases eligible for the primary endpoint: 1 case and 2 cases, respectively. All 3 of the cases were in the control group.

Due to the rapid accumulation of cases prior to database cut-off, 98 cases from participants randomised between SDSD and control were included in the interim analysis. The alpha level for the interim analysis calculated from the gamma (-2.5) alpha-spending function was 4.16% based the actual number of SDSD cases at the interim, meaning inferences on the primary endpoint were made using 95.84% confidence intervals. Whilst alpha was determined based on the 98 cases from participants who received SDSD, the primary analysis was prespecified to include participants who received either LDSD or SDSD (131 cases).

Study population

The efficacy population included a total of 11,636 individuals, 5807 in the test group and 5829 in the control group.

The disposition of the participants for the efficacy analysis is summarised below.



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

The dosing schedule and baseline characteristics of the primary analysis set are summarised hereafter.

Table 5: Dosing intervals (SDSD + LDSD Seronegative for Efficacy Analysis Set)

	Parameter	AZD1222 (N = 5807)	Control (N = 5829)
Dose schedule n(%)	< 6 weeks	1702 (29.3)	1698 (29.1)
	6-8 weeks	568 (9.8)	527 (9.0)
	9-11 weeks	1444 (24.9)	1488 (25.5)
	12+ weeks	2093 (36.0)	2116 (36.3)

Table 6: Demographics (SDSD + LDSD Seronegative for Efficacy Analysis Set)

Characteristic	Statistics	AZD1222 (N =5807)	Control (N = 5829)	Total (N = 11636)
Age (years) at screening	n	5807	5829	11636
	Mean	41.56	41.48	41.52
	SD	12.72	12.65	12.68
	Median	40.00	40.00	40.00
	Min	18.0	18.0	18.0
	Max	86.0	88.0	88.0
Age group at screening, n (%)				
	18 to 64 years	5466 (94.1)	5510 (94.5)	10976 (94.3)
	≥ 65 years	341 (5.9)	319 (5.5)	660 (5.7)
	18 to 55 years	5089 (87.6)	5129 (88.0)	10218 (87.8)
	56 to 69 years	494 (8.5)	480 (8.2)	974 (8.4)
	≥ 70 years	224 (3.9)	220 (3.8)	444 (3.8)
Sex, n (%)	Female	3525 (60.7)	3521 (60.4)	7046 (60.6)
	Male	2282 (39.3)	2307 (39.6)	4589 (39.4)
	Transgender	0	1 (<0.1)	1 (<0.1)

[a] Each race category counts participants who selected that category. Arab is counted under white.

Table 7: Baseline characteristics (SDSD + LDSD Seronegative for Efficacy Analysis Set)

Characteristic	Statistics	AZD1222 (N=5807)	Control (N=5829)	Total (N=11636)
Respiratory disease n (%)	Yes	658 (11.3)	705 (12.1)	1363 (11.7)
	No	5149 (88.7)	5124 (87.9)	10273 (88.3)
COPD (including chronic bronchitis and emphysema)	Yes	5 (0.1)	6 (0.1)	11 (0.1)
Bronchiectasis	Yes	4 (0.1)	5 (0.1)	9 (0.1)
Asthma	Yes	434 (7.5)	476 (8.2)	910 (7.8)
Other	Yes	68 (1.2)	67 (1.1)	135 (1.2)
Respiratory disease with missing subcategory	Yes	147 (2.5)	151 (2.6)	298 (2.6)
Diabetes n (%)	Yes	135 (2.3)	135 (2.3)	270 (2.3)
	No	5672 (97.7)	5694 (97.7)	11366 (97.7)
Type 1 Diabetes	Yes	12 (0.2)	10 (0.2)	22 (0.2)
Type 2 diabetes not using insulin	Yes	61 (1.1)	58 (1.0)	119 (1.0)
Type 2 diabetes using insulin	Yes	6 (0.1)	3 (0.1)	9 (0.1)
Other	Yes	28 (0.5)	29 (0.5)	57 (0.5)
Diabetes with missing subcategory	Yes	28 (0.5)	35 (0.6)	63 (0.5)
Comorbidity at baseline[a] n (%)	Yes	2070 (35.6)	2133 (36.6)	4203 (36.1)
	No	3733 (64.3)	3683 (63.2)	7416 (63.7)
	Missing	4 (0.1)	13 (0.2)	17 (0.1)
Body Mass Index (BMI) (kg/m^2)	n	4432	4444	8876
	Mean	26.37	26.52	26.44
	SD	5.116	5.143	5.130
	Median	25.50	25.50	25.50
	Min	13.3	11.4	11.4
	Max	95.6	64.1	95.6
BMI category n (%)	< 30 kg/m2	3543 (79.8)	3516 (78.9)	7059 (79.4)
	>= 30 kg/m2	889 (20.0)	928 (20.8)	1817 (20.4)
	Missing	8 (0.2)	11 (0.2)	19 (0.2)
Serostatus at Day 0 n (%)	Negative	4440 (100)	4455 (100)	8895 (100)
Cardiovascular Disorder n (%)	Yes	535 (12.0)	510 (11.4)	1045 (11.7)
	No	3905 (88.0)	3945 (88.6)	7850 (88.3)
Chronic heart failure	Yes	0	1 (<0.1)	1 (<0.1)
Ischaemic heart disease (including angina)	Yes	7 (0.2)	8 (0.2)	15 (0.2)
Atrial fibrillation	Yes	11 (0.2)	12 (0.3)	23 (0.3)
Peripheral vascular disease	Yes	1 (<0.1)	3 (0.1)	4 (<0.1)
Valvular heart disease	Yes	7 (0.2)	11 (0.2)	18 (0.2)
Hypertension	Yes	264 (5.9)	244 (5.5)	508 (5.7)
Myocardial infarction	Yes	9 (0.2)	5 (0.1)	14 (0.2)
Other	Yes	101 (2.3)	94 (2.1)	195 (2.2)
Cardiovascular disorder with missing subcategory	Yes	135 (3.0)	132 (3.0)	267 (3.0)

The age in the primary analysis population ranged from 18 to 88 years, with a median of 40 years; 88% of the population were adults between 18 and 55 years of age, 8% between 55 and 69 years, and 4% ≥ 70 years. The population included a majority of female subjects (61%) and a vast majority of White subjects (83%) with 4% of Asian and 4% of Black people. The proportion of subjects with comorbidities was substantial (36%): obesity (20%); cardiovascular disease (11%), mainly hypertension (5%); respiratory disease (12%), mainly asthma (8%); and diabetes (2%).

Primary efficacy endpoint

Out of the 131 COVID-19 cases, 30 were reported in the vaccine group and 101 in the placebo group. The point estimate for VE was 70.4% with a 95.84% confidence interval ranging from 54.8 to 80.6%. The pre-specified criterion for study success was met; the lower bound of the 95.84% confidence interval was above 20%. The point estimate was above 50% and the confidence interval lower bound above 30%, so efficacy was also shown in line with

the target profile outlined by WHO for COVID-19 vaccines.

Table 8: Vaccine efficacy for incidence of first SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥ 15 days post second vaccine dose in participants seronegative at baseline

	Participants with events				VE (%)	95.84% CI (%)
	AZD1222		Control			
	N	n (%)	N	n (%)		
Primary endpoint	5807	30 (0.52)	5829	101 (1.73)	70.42	(54.84, 80.63)

Efficacy was also shown if only the subgroup of participants randomised between SDSD and control were considered (VE=62.10%, 95.84% CI [39.96, 76.08]). In the subgroup randomised between LDSD and control, VE was 90.05%, 95.84% CI (65.84, 97.10).

The results were consistent in the subgroup of participants with a comorbidity at baseline, where a comorbidity is defined as BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes (VE=73.4%, 95% CI [48.5, 86.3]), and in the UK alone (VE=73.5%, 95% CI [55.5, 84.2]).

There is limited information available on efficacy in participants aged 65 or over, although there is nothing to suggest lack of protection. In this subpopulation, there were only two COVID-19 cases in the primary analysis. When considering all cases from dose 1, there were 2 cases on AZD1222 compared to 8 on control (VE=76%), although this result was associated with a wide confidence interval.

Only one COVID-19 case (in the control group) was reported in participants seropositive at baseline.

Severe cases and hospitalisations

There was only 1 severe COVID-19 case in the primary efficacy analysis (from 15 days after dose 2) in the control group. Even considering all cases from dose 1 there were only 2 severe cases, both in the control group.

There were 5 hospitalisations in the primary efficacy analysis, all on control. Considering all cases from dose 1, there were 2 hospitalisations in the AZD1222 group and 16 in the control group providing some evidence of an effect of the vaccine on COVID-19-related hospitalisations with a CI lower bound above 30% (VE=87.59%; 95% CI 46.03, 97.15). Both hospitalisations in the AZD1222 group were before 22 days after dose 1, as were 7 of the 16 in the control group. The two cases of hospitalisation in the AZD1222 group occurred on days 1 and 10 post vaccination.

Asymptomatic cases

Participants in the COV002 study had weekly self-swabs using the central NHS Pillar 2 testing mechanism. Analyses including asymptomatic cases demonstrated that the overall incidence of infections was decreased, not just the incidence of symptomatic COVID-19, thereby suggesting an effect on transmission as well.

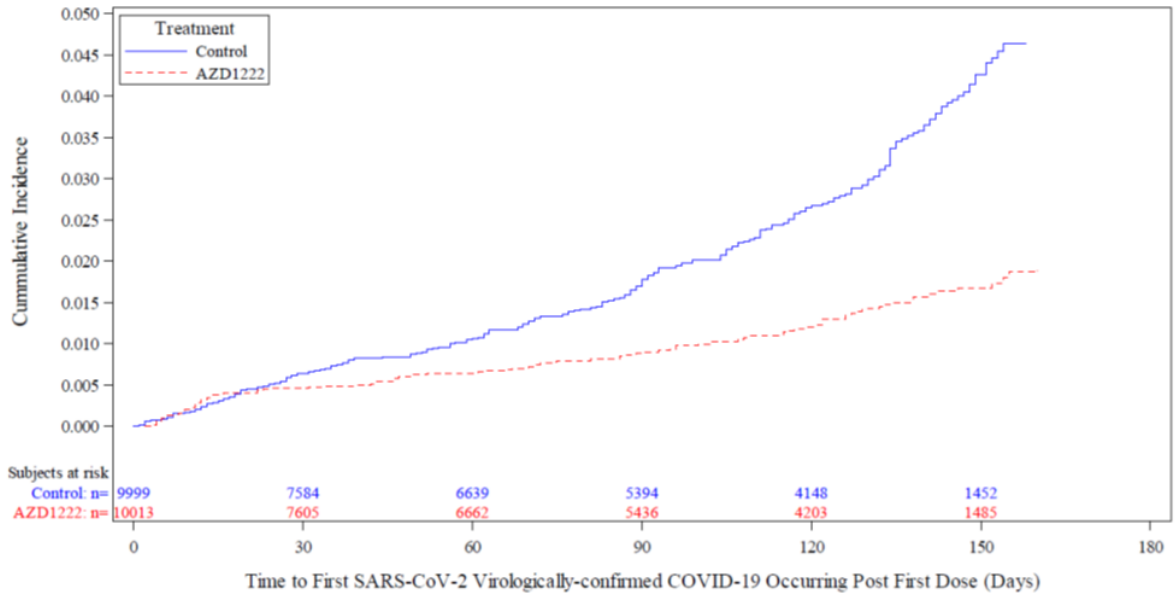
Table 9: Vaccine efficacy for incidence of first SARS-CoV-2 symptomatic or symptomatic infection occurring ≥ 15 Days post second vaccine dose in participants seronegative at baseline

	Participants with events		VE (%)	95.84% CI (%)
	AZD1222 (N=3744)	Control (N=3804)		
	n (%)	n (%)		
Symptomatic	18 (0.48)	68 (1.79)	73.52	(55.50, 84.24)
Asymptomatic	29 (0.77)	40 (1.05)		
Total	47 (1.26)	108 (2.84)	56.46	(38.74, 69.05)

Onset of protection

The early onset of protection is illustrated in the figure below, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants. Disease incidence is similar in the vaccine and placebo arms until approximately 21 days after Dose 1, at which point the curves diverge, with cases accumulating at a faster rate in the control group compared to the AZD1222 group.

Figure 1: Cumulative incidence plot for time to first SARS-CoV-2 virologically-confirmed COVID-19 occurring post first vaccine dose



Protection after the first vaccine dose

Exploratory analyses were conducted to investigate whether protective immunity was induced by the first dose and what the duration of protection was. The follow-up time began at 22 days after the first dose and was censored at the time of the second dose. Results indicated that the first dose provided protective immunity at least until 12 weeks.

Table 10: Vaccine efficacy for incidence of first SARS-CoV-2 virologically-confirmed COVID-19 occurring post first dose + 22 Days and before second dose of vaccine

	Participants with events				VE (%)	95% CI
	AZD1222		Control			
	N	n (%)	N	n (%)		
Cases to Week 12	7998	12 (0.15)	7982	44 (0.55)	73.00	(48.79, 85.76)

Effect of dose interval on VE ≥ 15 days after dose 2
The dataset in which efficacy of a two-dose regimen had been demonstrated contained data over a wide range of dose intervals (4 to 26 weeks): 29.3% were < 6 weeks, 34.7% were 6-11 weeks, and 36.0% were ≥ 12 weeks.

Subgroup analyses were conducted of vaccine efficacy by dosing interval. In line with immunogenicity data where increases in the binding and neutralising antibody responses were observed with increased dosing interval, efficacy was demonstrated with more certainty for dose intervals from 8-12 weeks. For the subgroup with dosing interval 8-11 weeks, VE was 72.85%, 95% CI (43.45, 86.97), for the subgroup with dosing interval > 11 weeks, it was 81.90%, 95% CI (59.93, 91.90). Exploratory subgroup analyses showed vaccine efficacy around 80% for longer dosing intervals, but data were limited and estimates were associated with wide confidence intervals.

Efficacy of using an initial half dose
A proportion of participants received a half dose of vaccine for their first administration. Participants were not randomised between receiving a half dose (LD) or the standard dose (SD) for the first dose, and because of other confounding factors, it is not possible to confidently compare results from the two different dosing regimens. Such factors include differences in the dosing interval (generally longer for LD), population studied (younger population for LD), country (UK only for LD) and stage of pandemic (participants receiving LD were initially dosed at a time when the incidence of cases in the UK was low). There is not persuasive evidence of a real difference in VE between SD and LD, and the apparent difference is considered more likely to be the result of confounding factors, especially the dosing interval. Conclusions on vaccine efficacy were primarily based on the pre-planned primary analysis including both SD and LD participants, and not on subgroups.

IV.5 Clinical safety

Safety population and exposure

The any dose safety analysis set comprises 23,745 subjects, pooled from the 4 multicentre trials, that received at least one dose of study intervention up to the data cut-off 04 November 2020. Of these, 12021 received at least one dose of AZD1222; 8266 received 2 doses of which 6568 were SDSD. Approximately one third of subjects each had a dose schedule in the range of < 6 weeks, 6 to 11 weeks, or ≥ 12 weeks.

Table 11: Study drug exposure (any dose safety analysis set)

	Parameter	**AZD1222** (N = 12021)	**Control** (N = 11724)
Dose level[a] n (%)	LDSD	1516 (12.6)	1472 (12.6)
	LDLD	127 (1.1)	69 (0.6)
	SDSD	6568 (54.6)	6472 (55.2)
	SDLD	55 (0.5)	36 (0.3)
	LD	305 (2.5)	281 (2.4)
	SD	3450 (28.7)	3394 (28.9)
	Total	12021	11724
Number of doses n (%)	1	3755 (31.2)	3675 (31.3)
	2	8266 (68.8)	8049 (68.7)
	Total	12021	11724
Dose schedule n (%)	< 6 weeks	3412 (41.3)	3234 (40.2)
	6-8 weeks	680 (8.2)	604 (7.5)
	9-11 weeks	1558 (18.8)	1550 (19.3)
	12+ weeks	2616 (31.6)	2661 (33.1)
	Total	8266	8049

SD = Standard dose; LD = Low dose

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

The median duration of follow-up in the AZD1222 group was 105 days post-dose 1, and 62 days post-dose 2.

The baseline demographics and characteristics of the safety population are presented below in Table 12. Overall these were balanced between the 2 study groups.

Table 12: Baseline demographics and characteristic (any dose safety analysis set)

Characteristic	Statistics	AZD1222 (N = 12021)	Control (N = 11724)	Total (N = 23745)
Age group at screening, n (%)	18 to 64 years	10852 (90.3)	10783 (92.0)	21635 (91.1)
	≥ 65 years	1169 (9.7)	940 (8.0)	2109 (8.9)
	18 to 55 years	9802 (81.5)	9788 (83.5)	19590 (82.5)
	56 to 69 years	1398 (11.6)	1296 (11.1)	2694 (11.3)
	≥ 70 years	821 (6.8)	639 (5.5)	1460 (6.1)
Sex, n (%)	Female	6711 (55.8)	6550 (55.9)	13261 (55.8)
	Male	5310 (44.2)	5171 (44.1)	10481 (44.1)
	Transgender	0	1 (<0.1)	1 (<0.1)
	Missing	0	2 (<0.1)	2 (<0.1)
Race[a], n (%)	White	9081 (75.5)	8887 (75.8)	17968 (75.7)
	Asian	425 (3.5)	371 (3.2)	796 (3.4)
	Black	1211 (10.1)	1210 (10.3)	2421 (10.2)
	Other	798 (6.6)	752 (6.4)	1550 (6.5)
	Mixed	489 (4.1)	483 (4.1)	972 (4.1)
	Unknown	16 (0.1)	17 (0.1)	33 (0.1)
	Missing	1 (<0.1)	4 (<0.1)	5 (<0.1)
BMI category n (%)	<30 kg/m2	9305 (77.4)	8998 (76.7)	18303 (77.1)
	≥30 kg/m2	2308 (19.2)	2318 (19.8)	4626 (19.5)
	Missing	408 (3.4)	408 (3.5)	816 (3.4)

Serostatus at Day 0 n (%)	Negative Positive Missing	11445 (95.2) 345 (2.9) 231 (1.9)	11139 (95.0) 373 (3.2) 212 (1.8)	22584 (95.1) 718 (3.0) 443 (1.9)
Cardiovascular disorder n (%)	Yes No Missing	1540 (12.8) 10477 (87.2) 4 (<0.1)	1435 (12.2) 10287 (87.7) 2 (<0.1)	2975 (12.5) 20764 (87.4) 6 (<0.1)
Respiratory disease n (%)	Yes No Missing	1253 (10.4) 10764 (89.5) 4 (<0.1)	1229 (10.5) 10493 (89.5) 2 (<0.1)	2482 (10.5) 21257 (89.5) 6 (<0.1)
Diabetes n (%)	Yes No Not collected[b] Missing	39 (2.8) 11142 (92.7) 534 (4.4) 6 (<0.1)	290 (2.5) 10898 (93.0) 533 (4.5) 3 (<0.1)	629 (2.6) 22040 (92.8) 1067 (4.5) 9 (<0.1)
Comorbidity at baseline[c] n (%)	Yes No Missing	4293 (35.7) 6977 (58.0) 751 (6.2)	4217 (36.0) 6764 (57.7) 743 (6.3)	8510 (35.8) 13741 (57.9) 1494 (6.3)
Current smoker n (%)	Yes No Missing	991 (8.2) 11026 (91.7) 4 (<0.1)	1034 (8.8) 10682 (91.1) 8 (0.1)	2025 (8.5) 21708 (91.4) 12 (0.1)

[a]Each race category counts participants who selected that category. Arab is counted under white
[b] COV001 does not collect this information; participants are counted in category 'Not collected'
[c]Cormorbidy at baseline = Yes if any comorbidity at baseline (BMI ≥30 kg/m2, cardiovascular disorder, respiratory disease or diabetes) is yes.

There were more females (56%) than males. Twenty-four percent of subjects were from ethnic minority backgrounds. The majority of subjects in the safety population were in the younger age group 18-55 years (83%). Of the 1169 (9%) subjects in the AZD1222 group that were ≥65 years of age, 668 received 2 doses, of which 586 were SDSD. Overall three percent of subjects were seropositive at baseline, the percentage was highest in South Africa (14.8%) and much lower in Brazil (2.3%) and the UK (1.6%). Just over one third of subjects had at least one comorbidity at baseline. The most common comorbidities were obesity, hypertension and asthma.

Local and systemic reactogenicity

Solicited adverse events (AEs) were collected via a diary card for 7 days following each vaccination in a subset of 6,137 subjects, mainly from the UK and South Africa. Of these, 5145 were in the Dose 1 SD subset (Table 13). There were some differences in how reactogenicity data was collected in the South African trial, in particular, solicited AEs were collected until Day 6 instead of day 7, there was no grade 4 severity option and fewer AE terms were solicited.

Table 13: Reactogenicity population by subgroup (Dose 1 SD reactogenicity subset)

Subpopulation	**Number of Participants evaluated for solicited AEs**	
	AZD1222 (N=2648)	**Control (N=2497)**
Country		
UK	1636	1497
Brazil	100	99
South Africa	912	901
Comorbidity		
Yes	822	775

No	1393	1308
Serostatus at baseline		
Positive	160	179
Negative	2387	2224
Age		
18-64 years	2245	2172
≥ 65 years	403	325

In the AZD1222 Dose 1 SD group, 2580 subjects were evaluated for solicited AEs after vaccination 1 and 1662 subjects after vaccination 2, of which 400 and 266 respectively were ≥65 years of age. A slightly higher percentage of subjects were seropositive at baseline compared with the overall safety population, which likely reflects the higher number of subjects that were seropositive at baseline in South Africa.

An overall summary of solicited AEs in the dose 1 SD safety analysis set is provided in table 14 below.

Table 14: Overall summary of solicited AEs (Dose 1 SD safety analysis set)

Participants*	**Days 0 to 7 After Any Dose**		**Days 0 to 7 After First Dose**		**Days 0 to 7 After Second Dose**	
	AZD1222 (N=10069)	**Control (N=9902)**	**AZD1222 (N=10069)**	**Control (N=9902)**	**AZD1222 (N=10069)**	**Control (N=9902)**
Evaluated for solicited AEs, n	2648	2497	2580	2425	1662	1526
Any solicited AE, n (%)	2277 (86.0)	1791 (71.7)	2161 (83.8)	1637 (67.5)	1026 (61.7)	722 (47.3)
Any solicited local AE, n (%)	1979 (74.7)	1258 (50.4)	1839 (71.3)	1117 (46.1)	778 (46.8)	456 (29.9)
Any ≥ Grade 3 severity solicited local AE, n (%)	252 (9.5)	138 (5.5)	210 (8.1)	112 (4.6)	70 (4.2)	38 (2.5)
Any solicited systemic AE, n (%)	1932 (73.0)	1488 (59.6)	1817 (70.4)	1320 (54.4)	741 (44.6)	545 (35.7)
Any ≥ Grade 3 severity solicited systemic AE, n (%)	221 (8.3)	63 (2.5)	192 (7.4)	41 (1.7)	37 (2.2)	27 (1.8)

*Participants with multiple events in the same category are counted once in that category. Participants with events in more than 1 category are counted once in each of those categories. Denominators used in the percentage calculations are the number of participants "Evaluated for solicited AEs".
Solicited AEs were assessed daily after vaccination from Day 0 to Day 6 for COV0005 and to Day 7 for rest of studies via e-diary or diary card.
No grade 4 severity option for events collected in COV005. Pain and warmth, malaise, nausea and vomiting were not assessed for COV005. Induration, feverishness and chills did not include COV005 since no severity grading collected. For redness, swelling and fever severity grading was derived based on reported value. Bruising only collected for COV005.

Overall, 86% of subjects in the AZD1222 group (Days 0-7 after any vaccination) experienced at least one solicited AE compared to 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the AZD1222 group experienced at least one grade ≥3 local solicited AE and 8% at least one grade ≥3 systemic solicited event compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose compared with the first.

Table 15: Summary of Local Solicited Adverse Events (Dose 1 SD safety analysis set) – Days 0-7 after any vaccination

Local solicited Adverse Events/ Severity	AZD1222 (N = 10069)	Control (N = 9902)
Participants with any local solicited AE	1979 (74.7)	1258 (50.4)
1: Mild	1382 (52.2)	967 (38.7)
2: Moderate	345 (13.0)	153 (6.1)
3: Severe	252 (9.5)	138 (5.5)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Pain	941 (54.2)	586 (36.7)
1: Mild	776 (44.7)	522 (32.7)
2: Moderate	156 (9.0)	61 (3.8)
3: Severe	9 (0.5)	3 (0.2)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596
Tenderness	1688 (63.7)	987 (39.5)
1: Mild	1398 (52.8)	902 (36.1)
2: Moderate	258 (9.7)	78 (3.1)
3: Severe	32 (1.2)	7 (0.3)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Redness	368 (14.0)	218 (8.8)
1: 2.5-5 cm	176 (6.7)	123 (5.0)
2: 5.1-10 cm	67 (2.6)	36 (1.5)
3: >10 cm	125 (4.8)	59 (2.4)
4: Necrosis or ED	0 (0.0)	0 (0.0)
Total participants evaluated	2626	2480
Warmth	308 (17.7)	232 (14.5)
1: Mild	301 (17.3)	223 (14.0)
2: Moderate	7 (0.4)	9 (0.6)
3: Severe	0 (0.0)	0 (0.0)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596
Itch	335 (12.7)	187 (7.5)
1: Mild	272 (10.3)	156 (6.2)
2: Moderate	53 (2.0)	26 (1.0)
3: Severe	10 (0.4)	5 (0.2)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Swelling	262 (10.0)	145 (5.8)
1: 2.5-5 cm and no IwA	96 (3.7)	52 (2.1)
2: 5.1-10 cm or IwA	28 (1.1)	26 (1.0)
3: >10 cm or PDA	138 (5.3)	67 (2.7)
4: Necrosis	0 (0.0)	0 (0.0)
Total participants evaluated	2626	2481

Local solicited Adverse Events/ Severity	AZD1222 (N = 10069)	Control (N = 9902)
Induration	164 (9.4)	136 (8.5)
1: 2.5-5 cm and no IwA	66 (3.8)	52 (3.3)
2: 5.1-10 cm or IwA	27 (1.6)	27 (1.7)
3: >10 cm or PDA	71 (4.1)	57 (3.6)
4: Necrosis	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596
Bruising	158 (17.3)	60 (6.7)
1: <10 mm	123 (13.5)	48 (5.3)
2: 10-25 mm	28 (3.1)	8 (0.9)
3: >25 mm	7 (0.8)	4 (0.4)
Total participants evaluated	912	901

Abbreviations: AE = Adverse Event, ED = Exfoliative dermatitis; ER=Emergency department; IwA = Interfere with activity; PDA = Prevent daily activity.
Total participants evaluated was used as 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 6 for COV005 and to Day 7 for rest of studies via e-diary or diary card.
No grade 4 severity option for events collected in COV005. Pain and warmth were not assessed for COV005. Induration did not include COV005 as grading scale was not compatible.
For redness and swelling, severity grading was derived based on reported value. Bruising only collected for COV005.

The most frequently reported local solicited AEs in the AZD1222 Dose 1 SD group after any vaccination were tenderness (64%) and pain (54%). The most comment events of Grade ≥3 were swelling (5%) and redness (5%). No grade 4 AEs were reported.

Table 16: Summary of Systemic Solicited Adverse Events (Dose 1 SD safety analysis set) – Days 0-7 after any vaccination

Systemic Solicited Adverse Events/ Severity	AZD1222 (N = 10069)	Control (N = 9902)
Participants with any systemic solicited AE	1932 (73.0)	1488 (59.6)
1: Mild	973 (36.7)	1022 (40.9)
2: Moderate	738 (27.9)	403 (16.1)
3: Severe	220 (8.3)	63 (2.5)
4: ER or hospitalization	1 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Fever	208 (7.9)	31 (1.2)
1: 38.0 - 38.4°C	122 (4.6)	18 (0.7)
2: 38.5 - 38.9°C	67 (2.5)	6 (0.2)
3: 39.0 - 40°C	18 (0.7)	7 (0.3)
4: >40°C	1 (0.0)	0 (0.0)
Total participants evaluated	2644	2493
Feverishness	583 (33.6)	171 (10.7)
1: Mild	270 (15.6)	153 (9.6)
2: Moderate	252 (14.5)	16 (1.0)
3: Severe	61 (3.5)	2 (0.1)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596

Systemic Solicited Adverse Events/ Severity	AZD1222 (N = 10069)	Control (N = 9902)
Chills	554 (31.9)	132 (8.3)
1: Mild	278 (16.0)	115 (7.2)
2: Moderate	216 (12.4)	17 (1.1)
3: Severe	60 (3.5)	0 (0.0)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596
Joint pain	698 (26.4)	310 (12.4)
1: Mild	492 (18.6)	250 (10.0)
2: Moderate	176 (6.6)	48 (1.9)
3: Severe	30 (1.1)	12 (0.5)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2496
Muscle pain	1164 (44.0)	540 (21.6)
1: Mild	797 (30.1)	452 (18.1)
2: Moderate	317 (12.0)	79 (3.2)
3: Severe	50 (1.9)	9 (0.4)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2496
Fatigue	1407 (53.1)	955 (38.2)
1: Mild	856 (32.3)	704 (28.2)
2: Moderate	466 (17.6)	224 (9.0)
3: Severe	85 (3.2)	27 (1.1)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Headache	1394 (52.6)	975 (39.0)
1: Mild	901 (34.0)	743 (29.8)
2: Moderate	422 (15.9)	209 (8.4)
3: Severe	71 (2.7)	23 (0.9)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	2648	2497
Malaise	768 (44.2)	323 (20.2)
1: Mild	417 (24.0)	252 (15.8)
2: Moderate	285 (16.4)	64 (4.0)
3: Severe	66 (3.8)	7 (0.4)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596
Nausea	380 (21.9)	209 (13.1)
1: Mild	291 (16.8)	173 (10.8)
2: Moderate	74 (4.3)	34 (2.1)
3: Severe	15 (0.9)	2 (0.1)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596

Systemic Solicited Adverse Events/ Severity	AZD1222 (N = 10069)	Control (N = 9902)
Vomiting	29 (1.7)	14 (0.9)
1: Mild	14 (0.8)	8 (0.5)
2: Moderate	9 (0.5)	4 (0.3)
3: Severe	6 (0.3)	2 (0.1)
4: ER or hospitalization	0 (0.0)	0 (0.0)
Total participants evaluated	1736	1596

Abbreviations: AE = Adverse Event, ER=Emergency department.
Total participants evaluated was used as 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.
No grade 4 severity option for events collected in COV005. Malaise, Nausea and Vomiting were not assessed for COV005. Feverish and Chills did not include COV005 since no severity grading collected.
For Fever, severity grading was derived based on reported value.

The most frequently reported systemic solicited AEs in the AZD1222 Dose 1 SD group after any vaccination were fatigue (53%) and headache (53%). The most comment events of Grade ≥3 were malaise (4%) and chills (4%). One grade 4 event of fever >40° was reported after vaccination 1.

All of the local and systemic solicited events were reported more commonly in the AZD1222 Dose 1 SD group compared with the control, including in the UK where active control was used for both doses, and are considered ADRs for AZD1222. This is reflected in the Information for Healthcare Professionals and the Information for UK recipients.

The incidence of subjects with at least one local or systemic solicited event after any vaccination was highest on day 1 following vaccination, decreasing to 4% and 13 %, respectively, by day 7. The most common systemic solicited AEs at day 7 were fatigue, headache and malaise. Only 0.7% and 0.2% of subjects had a local or systemic solicited AE grade ≥3 at day 7 respectively.

Data on solicited AEs by dosing interval were provided. However, this is difficult to interpret. Whilst post dose 2 the incidence of solicited AEs appeared lower in subjects with a dosing window <6 weeks, this pattern was also seen post dose 1 and may reflect potential differences in the population. No increase in the incidence of local or systemic solicited AEs ≥ grade 3 was observed after vaccination 2 between subjects that had a dosing interval less or more than 6 weeks.

The number of subjects in the reactogenicity subset that were seropositive at baseline is small limiting any firm conclusions that can be drawn. Except for a higher rate of subjects with any ≥ grade 3 local solicited AE (15% vs 9%), the incidence of solicited AEs in the dose 1 SD AZD1222 group was similar in the seropositive and seronegative subjects. No seropositive subjects reported a grade 4 solicited AE, one grade 4 solicited AE (fever) was reported in the seronegative group.

With regards to age, the number of subjects evaluated for solicited AEs in the ≥65 years group are relatively small. Whilst a similar percentage of subjects in the 18-64 years and ≥65 years reported at least one solicited AE, fewer subjects in the ≥65 years reported a local or systemic solicited AE, or any ≥ grade 3 solicited AE.

Currently there are insufficient data to support a recommendation for use of prophylactic paracetamol. However, information is included in the Information for Healthcare Professionals and the Information for UK recipients regarding symptomatic use of

paracetamol-containing products.

Adverse events

Unsolicited AEs were collected through 28 days post each dose. The overall incidence after any vaccination with any dose was higher in the AZD1222 group (38%) compared to the control (28%). However, the overall incidence of unsolicited AEs reported >7 days after any dose was similar between the 2 groups. Most of the unsolicited AEs were mild to moderate in severity. The incidence of unsolicited AEs with severity ≥ Grade 3 reported within 28 days after any dose was low (< 2%) and similar between the 2 groups.

The most frequently reported AEs, occurring in ≥2% of the AZD1222 group, were consistent with AEs commonly observed following vaccination. These predominantly occurred ≤ 7 days of any dose. There were no AEs with an incidence ≥ 2% reported > 7 days of any dose.

Adverse event data were evaluated at the preferred term level, and with reference to AE listings which included information on onset, duration, severity, seriousness and relatedness. AEs by System Organ Class (SOC) are summarised below:

Table 17: Unsolicited Adverse Events by System Organ Class (Any dose for safety analysis set)

	Number (%) of Participants[a]	
System Organ Class	**AZD1222 (N= 12021)**	**Control (N = 11724)**
Participants with any unsolicited AE	4539 (37.8)	3266 (27.9)
System Organ Class uncoded	85 (0.7)	78 (0.7)
Infections and infestations	348 (2.9)	364 (3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (<0.1)	11 (<0.1)
Blood and lymphatic system disorders	40 (0.3)	46 (0.4)
Immune system disorders	14 (0.1)	16 (0.1)
Metabolism and nutrition disorders	41 (0.3)	34 (0.3)
Psychiatric disorders	66 (0.5)	45 (0.4)
Nervous system disorders	1408 (11.7)	918 (7.8)
Eye disorders	68 (0.6)	49 (0.4)
Ear and labyrinth disorders	42 (0.3)	42 (0.4)
Cardiac disorders	30 (0.2)	21 (0.2)
Vascular disorders	61 (0.5)	59 (0.5)
Respiratory, thoracic and mediastinal disorders	401 (3.3)	422 (3.6)
Gastrointestinal disorders	577 (4.8)	414 (3.5)
Hepatobiliary disorders	1 (<0.1)	3 (<0.1)
Skin and subcutaneous tissue disorders	180 (1.5)	140 (1.2)
Musculoskeletal and connective tissue disorders	1261 (10.5)	627 (5.3)
Renal and urinary disorders	26 (0.2)	25 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (<0.1)	0
Reproductive system and breast disorders	44 (0.4)	35 (0.3)
Congenital, familial and genetic disorders	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	3049 (25.4)	1759 (15.0)
Investigations	205 (1.7)	115 (1.0)
Injury, poisoning and procedural complications	87 (0.7)	90 (0.8)

Social circumstances	2 (<0.1)	1 (<0.1)

[a] Number (%) of participants with AEs, sorted on international order for system organ class. Participants with multiple events in the same preferred term are counted only once in each of those preferred term. Participants with events in more than 1 preferred term are counted once in each of those preferred term. Unsolicited AEs summarized from the start of each dose until Day 28. Unevaluable event is an event with pending query at the time of the interim analysis database lock.

The imbalance in the SOC of *Nervous system disorders* was mainly driven by 'headache' events, reported by 9.3% subjects after AZD1222 vs 6.1% after control. There were also imbalances in events of 'lethargy' (0.4% vs 0.2%) and 'somnolence' (0.3% vs 0.2%) which are captured by the adverse drug reaction (ADR) 'fatigue' (see '*General disorders and administration site conditions* below). A slight imbalance was seen in events of 'dizziness' (0.6% vs 0.5%) and it is noted that this is a known ADR for the control MenACWY vaccines. 'Headache' and 'dizziness' are included as ADRs in the Information for Healthcare Professionals and the Information for UK recipients

In addition, a detailed review of neurological AEs was undertaken which identified the following neurological cases of interest:

- A new diagnosis of multiple sclerosis in the AZD1222 group. Symptom onset was 10 days after first AZD1222 dose. MRI of the brain and spinal cord demonstrated multiple lesions. All but one of these lesions were not gadolinium-enhancing suggesting that most lesions pre-dated the AZD1222 dose.

- A likely case of 'short segment inflammatory myelitis' in the AZD1222 group, although the diagnosis is not certain. Symptom onset was 14 days after second AZD1222 dose.

  Based on the available data, the presence or the absence of a causative association between the AZD1222 vaccine and these two cases cannot be concluded with certainty.

- A case of 'transverse myelitis' in the control group. Symptom onset was 54 days after first control dose.

- Six cases of facial paralysis, three in each study group. The three cases in the AZD1222 group were all one-sided 'facial nerve palsies', two of which had features suggesting they were not related to AZD1222 vaccination (one case is considered related to chronic suppurative otitis media / mastoiditis, the other occurred 80 days after vaccination).

- Two cases of trigeminal neuralgia (both in the control group).

These cases and other potential neurological events are covered by the list of adverse events of special interest (AESIs) previously defined by the MHRA for inclusion as part of the RMP for any potential COVID-19 vaccine and will be subject to routine and additional pharmacovigilance measures. In addition, 'Neuroinflammatory disorders' is included in the RMP as an 'Important potential risk'. Section 4.8 of the HCP information reflects that "*Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established.'*

The imbalance in the SOC of *Gastrointestinal disorders* was mainly driven by events of 'diarrhoea' (1.3% vs 1.0%), 'nausea' (1.9% vs 1.2%) and 'vomiting' (0.7% vs 0.4%). In

addition, an imbalance in events of abdominal pain (0.4% vs 0.3%) and upper abdominal pain (0.2% vs 0.1%) was seen, particularly ≤7 days post any vaccination. Given the other ADRs in the gastrointestinal SOC, a relationship with AZD1222 is considered plausible. 'Diarrhoea', 'nausea', 'vomiting' and 'abdominal pain' are considered ADRs and are included in the Information for Healthcare Professionals and the Information for UK recipients.

The imbalance in the SOC of *Musculoskeletal and connective tissue disorders* was mainly driven by events of 'arthralgia' (1.4% vs 0.8%) and myalgia (7.6% vs 3.1%). These are considered ADRs and are included in the Information for Healthcare Professionals and the Information for UK recipients

The imbalance in the SOC of *General disorders and administration site conditions* was mainly driven by events of asthenia (2.2% vs 1.1%), chills (3.4% vs 0.9%), fatigue (4.8% vs 2.8%), malaise (2.3% vs 1.3%), pyrexia (7.5% vs 1.9%) and vaccination site pain (10.4% vs 6.5%). With the exception of 'asthenia', based on the local and systemic reactogenicity data these are all considered ADRs and are included in the Information for Healthcare Professionals and the Information for UK recipients. In view of the similarity of the terms 'asthenia' and 'fatigue', and given that 'fatigue' is included as an ADR with a frequency designation of 'very common', it is acceptable that 'asthenia' is not included as an ADR. In addition, an imbalance in cases of 'influenza-like illness' (1.0% vs 0.6%) was noted and this has also been included as an ADR.

The small imbalance in the SOC of *Investigations* was mainly driven by events of 'body temperature increased' (0.7% vs 0.1%) which is captured by the listed ADR 'pyrexia' (frequency 'very common').

Within the SOC *Skin and subcutaneous tissue disorders,* 0.4% of subjects in the AZD1222 group reported the event 'hyperhidrosis' compared with 0.2% in the control group. The majority of cases occurred ≤ 7 days post any dosing. The event 'pruritus' was reported by 0.2% of cases in both treatment groups. The majority of cases, particularly in the AZD1222 group, occurred ≤ 7 days post any dosing. Pruritus is a listed event for one of the 2 control MenACWY vaccines used. The event 'rash' was reported by 0.2% of cases in both treatment groups. Rash is a listed event for both of the control MenACWY vaccines used. 'Hyperhidrosis', 'pruritus' and 'rash' have been included as ADRs in the Information for Healthcare Professionals and the Information for UK recipients

Within the SOC *Blood and lymphatic system disorders,* 0.3% of subjects in both treatment groups reported the event 'lymphadenopathy'. Lymphadenopathy is known to be associated with vaccines and is related to the immune response. Lymphadenopathy is a listed event for one of the 2 control MenACWY vaccines used. Lymphadenopathy has been included as an ADR in the Information for Healthcare Professionals and the Information for UK recipients.

Within the SOC *Metabolism and nutrition disorders* the event 'decreased appetite' was reported by 0.2% subjects in the AZD1222 group and 0.1% in the control group. The majority of these events occurred ≤ 7 days post any dosing. Decreased appetite is a listed event for at least one of the 2 control MenACWY vaccines used. Decreased appetite has been included as an ADR in the Information for Healthcare Professionals and the Information for UK recipients.
No serious cases of *drug hypersensitivity* have been reported with AZD1222 up to the data cut-off. One case of anaphylaxis was reported, this occurred 63 days after vaccination and

was considered related to antibiotics. In addition, one event of angioedema was reported 8 days after vaccination and occurred after crab ingestion. One grade 1 AE of drug hypersensitivity was reported 11 days post vaccination. On the same day the subject reported a number of local grade 1 reactions and all AEs had a duration of 10 days. A MedDRA SMQ search of 'narrow hypersensitivity' revealed no imbalance in the percentage of subjects with at least one hypersensitivity AE. This remained the case if events including the listed ADR 'rash' were excluded. Hypersensitivity is not considered an ADR at present; however, reports of hypersensitivity will be kept under review.

A single case of erythema multiforme was reported 4 days post dose 2 in the AZD1222 group. This was grade 2 in severity, considered unlikely related to study medication by the investigator and was ongoing. However, in view of the proximity to dose 2, erythema multiforme will also be kept under review.

Subgroup data for unsolicited adverse events were provided by country, age, serostatus and comorbidity. In both the AZD1222 and control groups, the incidence of unsolicited AEs was higher in Brazil than in the UK or South Africa. This may in part reflect the fact that only 2% of the subjects in Brazil had solicited events collected, therefore more subjects may have reported typical reactogenicity AEs as unsolicited events. There is no indication of a worse safety profile in subjects aged ≥ 65 years, subjects who were seropositive at baseline or in subjects with at least one comorbidity.

Serious adverse events

Two deaths were reported in subjects that received AZD1222; one subject died 64 days after vaccination from *Pneumocystis jirovecii* pneumonia, they also had an AE of HIV test positive, and one subject died 86 days after their second dose of vaccine from metastatic ovarian cancer. Four deaths occurred in the control group (COVID-19 pneumonia, craniocerebral injury, injury, and homicide). None of the deaths were considered vaccine-related by the investigator.

Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% AZD1222, 0.8% control). There were no clear imbalances by SOC. The most frequently reported SAEs by SOC were 'Infections and Infestations' (0.1% vs 0.2%) and 'Injury, poisoning and procedural complications' (<0.1% vs 0.1%).

Only 5 SAEs were considered related by the investigator, of which 3 were in the AZD1222 group (pyrexia, C-reactive protein increased and transverse myelitis) and 2 were in the control group (autoimmune haemolytic anaemia, and myelitis). After the data cut-off, causality for the SAE of CRP increased was updated by the investigator to not treatment related. The case of pyrexia (40.5°) occurred 2 days after dose 1 of AZD1222. It was associated with increased sweating, shortness of breath, weakness, and loss of sense of smell and taste. The event was treated with paracetamol and resolved the same day. The case of transverse myelitis in the AZD1222 group and of myelitis in the control group are discussed in the 'Adverse events' section above. Overall within the SOC *Nervous system disorders'*, there were 7 SAEs in the AZD1222 group and 4 in the control group.

There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity).

Adverse events of special interest

AESI were based on the Brighton Collaborative case definitions (SPEAC 2020), clinical experience and scientific interest. AESI were grouped under neurological, vascular, haematological and immunological (including anaphylaxis and vaccine associated enhanced disease). The incidence of AESI was low and balanced between the two treatment groups.

Table 18: AESI by special interest category (any dose safety analysis set)

Special Interest Category	Number (%) of participants[a]	
	AZD1222 (N = 12021)	**Control (N = 11724)**
Participants with any AESI	95 (0.8)	126 (1.1)
Anaphylaxis	1 (<0.1)	0
Generalized convulsion	1 (<0.1)	1 (<0.1)
Neurologic events-other	64 (0.5)	79 (0.7)
Potential immune mediated conditions – Gastrointestinal disorders	1 (<0.1)	3 (<0.1)
Potential immune mediated conditions – Musculoskeletal disorders	1 (<0.1)	1 (<0.1)
Potential immune mediated conditions - Neuroinflammatory	5 (<0.1)	4 (<0.1)
Potential immune mediated conditions – Skin disorders	3 (<0.1)	4 (<0.1)
Potential immune mediated conditions – Vasculitides	0	1 (<0.1)
Potential immune mediated conditions – Other	3 (<0.1)	3 (<0.1)
Thrombotic, thromboembolic, and neurovascular events	4 (<0.1)	8 (<0.1)
VAERD	12 (0.1)	23 (0.2)

[a]Number (%) of participants with AEs, sorted in alphabetical order for special interest category. Participants with multiple events in the same preferred term are counted only once in each of those PTs. Participants with events in more than 1 PT are counted once in each of those PTs.

The non-serious event of anaphylaxis is discussed in the ‘Adverse events’ section above.

Vaccine associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD) is a theoretical risk, which is relevant to all COVID-19 vaccines. Currently, there are only 2 cases of severe COVID-19 that have been reported in the any dose efficacy set, both in the control group, limiting any conclusions that can be drawn. However, the type of immune response triggered by the vaccine (Th1 skewed) and the number of COVID-19 hospitalisations in the any dose efficacy set (2 vs 16) provides reassurance. It is recognised that VAERD may not become apparent until efficacy of the vaccine starts to wane. This is an important potential risk in the RMP and will be monitored via routine and additional pharmacovigilance activities.

There were no clinically meaningful imbalances in AESI incidence for any subgroup (country, age, serostatus or comorbidity).

Laboratory findings

Laboratory testing was only conducted in a subgroup of subjects up to 28 days after each dose. The incidence of decreases in white blood cells, neutrophils, and platelets was slightly higher in the AZD1222 group compared with control. However, there were very few unsolicited haematology or biochemistry adverse events reported and these were balanced between the 2 study groups.

Safety in special populations

Pregnancy and breastfeeding
Women who were pregnant or breastfeeding were excluded from the clinical trials. Pregnancy was reported for 21 subjects; 12 in the AZD1222 group and 9 in the control group. Of these pregnancies, 5 ended in spontaneous abortion – 2 in the AZD1222 group and 3 in the control group. Due to the limited duration of follow-up, the outcome of the remaining pregnancies is awaited. The results of preliminary studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or post-natal development; definitive animal studies have not been completed yet. The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established. Therefore, administration of COVID-19 Vaccine AstraZeneca in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus. It is unknown whether AZD1222 is excreted in breast milk

Information for Healthcare Professionals and the Information for UK recipients reflect these recommendations. Use in pregnancy and lactation is included in the RMP as missing information.

Paediatric population
In-line with the proposed indication, no data have been provided in subjects less than 18 years of age.

Immunosuppression
No data are currently available in immunocompromised subjects or in subjects taking immunosuppressants. Safety data is awaited in a subgroup of HIV positive subjects that were included in studies COV002 and COV005. This will be followed up in the RMP.

Safety related to interactions

No data are available on use with concomitant vaccines, including influenza vaccines.

Receipt of any vaccine, other than the study intervention within 30 days before and after each study vaccination, was an exclusion criterion in the clinical trials. In studies COV001 and COV002 there was an exception for licensed seasonal influenza and pneumococcal vaccinations. These were permitted at least 7 days before or after their study vaccine.

Discontinuations due to adverse events

No data were collected on adverse events leading to treatment or study withdrawal. However, the number of subjects who declined to receive a second dose of vaccine or withdrew early was balanced between the AZD1222 and control groups.

IV.6 Risk Management Plan (RMP)

Every new medicine that is authorised has a Risk Management Plan (RMP) in place to ensure the medicine is used as safely as possible. An RMP details important risks for the medicine and how more information can be obtained about these. This includes important identified risks which have been demonstrated to be associated with the medicine and require additional measures as part of the authorisation to minimise any potential risk to users. Important potential risks are those where there is a potential association with the product but the association has not been confirmed and further information needs to be collected to establish whether this risk exists. Missing information topics are typically those which have not been fully evaluated in the clinical trials, are relevant to the use of the product and require further information to be gathered.

The following section describes the RMP that has been agreed for the safe use of COVID-19 Vaccine AstraZeneca.

In addition to routine pharmacovigilance and risk minimisation measures, the MHRA has requested that all COVID-19 vaccines carry out further ad hoc pharmacovigilance activities specific to the pandemic situation. This includes more frequent safety signal detection activities with additional epidemiological analysis of potential safety signals and targeted safety events, frequent pharmacovigilance meetings with the MHRA, monthly pharmacovigilance safety update reports and batch specific surveillance.

The important identified risks, important potentials risks and missing information for the COVID-19 vaccine AstraZeneca are as follows:

Important Identified risk	None
Important potential risk	Neuroinflammatory disorders Vaccine-associated enhanced disease (VAED)
Missing information	Use of COVID-19 Vaccine AstraZeneca in pregnant and breastfeeding women Use of COVID-19 Vaccine AstraZeneca in subjects with severe immunodeficiency Use of COVID-19 Vaccine AstraZeneca in subjects with severe and/ or uncontrolled underlying disease Use of COVID-19 Vaccine AstraZeneca with other vaccines Long-term Effectiveness

There are no important identified risks for COVID-19 Vaccine AstraZeneca.

Neuroinflammatory disorders has been included as an important potential risk. Very rare events of neuroinflammatory disorders were reported in clinical trials following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established. The pharmacovigilance plan will further investigate whether there is a link between the vaccine and neuroinflammatory disorders.

Vaccine associated enhanced disease (VAED) has been included as a potential risk. This is a theoretical risk which is relevant to all COVID-19 vaccines based on VAED having been seen in animal models for vaccines developed for SARS-CoV-1 (a similar but not identical virus to SARS-CoV-2, the virus responsible for COVID-19). VAED has also been seen in association with use of another respiratory virus vaccine, the Respiratory syncytial virus (RSV) vaccine. There is currently no evidence from non-clinical or clinical data of an

association of VAED with COVID-19 Vaccine AstraZeneca; this potential risk will be further investigated as part of the pharmacovigilance plan for this vaccine.

Use in pregnant and breastfeeding women is included as missing information because this group was excluded from the clinical trials and further data need to be collected on the safety and efficacy of this use.

Use of COVID-19 Vaccine AstraZeneca in subjects with severe immunodeficiency is included as missing information as this group was excluded from the clinical trials and further data need to be collected on the safety and efficacy of this use.

Use of COVID-19 Vaccine AstraZeneca in subjects with severe and/ or uncontrolled underlying disease is included as missing information as this group was excluded from the clinical trials and further data need to be collected on the safety and efficacy of this use.

Use of COVID-19 Vaccine AstraZeneca with other vaccines when co-administered with other vaccines (either interchangeably with alternative licensed COVID-19 vaccines, or concurrently with seasonal illness vaccines) has not been evaluated. Further data need to be collected on the safety and efficacy of this use.

Vaccine efficacy for COVID-19 Vaccine AstraZeneca has been clearly demonstrated in clinical trials. Vaccine effectiveness relates to how well a vaccine works in the "real world" setting outside of clinical trials and being used in a wider variety of people. Therefore, long-term real-world data on vaccine effectiveness need to be collected and this has been included as a missing information topic.

The following studies have been proposed to gather more information on these topics:

Study	Summary of activity objectives	Safety concerns addressed	Status
• D8111R00003 • D8111R00004 • DSRU study (study code to be confirmed) Enhanced active surveillance A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222	Primary Objectives: • To assess the safety and tolerability of at least 1 dose of the AZD1222 in adults ≥ 18 years of age for a predefined period (eg, 3 months) after vaccination with first dose of AZD1222. Secondary Objectives: • To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 12 months after vaccination with first dose of AZD1222 Secondary Objectives (pregnancy sub-study): • To estimate the frequency of selected adverse pregnancy outcomes in women receiving the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception • To estimate the frequency of selected adverse fetal/neonatal outcomes at birth and up to 6 months of life in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception.	• Immune-mediated neurological conditions • Vaccine-associated enhanced disease • Use of AZD1222 in pregnant and breastfeeding women • Use of AZD1222 in subjects with severe immunodeficiency • Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease • Use of AZD1222 with other vaccines	Planned
AZD1222 Pregnancy Registry	Primary Objectives: • To estimate the frequency of selected adverse	• Use of AZD1222 in pregnant and breastfeeding	Planned

Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy	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, 60 days) before estimated date of conception • To estimate the frequency of selected adverse fetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 6 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, 60 days) before estimated date of conception.	women	
Post-marketing safety study A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns.	<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	• Immune-mediated neurological conditions • Vaccine-associated enhanced disease • Use of AZD1222 in pregnant and breastfeeding women • Use of AZD1222 in subjects with severe immunodeficiency • Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease • Use of AZD1222 with other vaccines	Planned
• D8111R00005 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	<u>Primary Objective:</u> • 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.	Vaccine effectiveness	Planned

The company is also planning an additional study to look at safety of COVID-19 Vaccine AstraZeneca in patients taking immunosuppressant medicines and with primary immunodeficiency.

The following ongoing pivotal clinical studies will also provide further safety data:

Study name and description **Status**	**Summary of objectives**
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	*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.
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	*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).
Study COV003 A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine • **Status**: Ongoing	*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.
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	*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.

IV.7 Discussion on the clinical aspects

Clinical immunogenicity

Although there are no defined immune correlates of protection against COVID-19, it is generally accepted that high-titre neutralising antibodies with a robust cytotoxic CD8+ T cell response and Th1-biased CD4+ effector response will be optimal for protective immunity after SARS-CoV-2 exposure.

AZD1222 elicits the rapid development of binding and neutralising antibodies after a priming dose, which are further increased with a booster dose to levels comparable to those measured in serum samples from convalescent patients.

The importance of the dosing interval is emphasised in the Phase III results. These seem to suggest that higher levels of antibodies are generated after a lower prime dose compared to the standard dose; however, this finding is confounded by the observation that the dose interval for the majority of participants in the standard dose group was shorter (< 6 weeks) than in the lower dose group (≥ 12 weeks). Antibody levels tend to increase as the interval between the prime and booster doses increases, so that, when considering antibody levels between lower and standard dose at the same intervals, there is no difference between the lower and standard dose.

There is a general concern about immunosenescence, and therefore, immunogenicity data in the older subgroups are critical. High seroconversion rates but lower GMTs were observed in the elderly (≥ 65 years) compared to younger adults, although the differences in the dosing interval may have partly confounded the results after the booster dose. Furthermore, the level of T cell responses was comparable in the elderly and younger age groups.

T cell responses are rapidly induced after the first dose of vaccine and are well maintained up to 28 days following the booster dose. The responses are heavily biased toward secretion of Th1 cytokines (IFN-γ, IL-2 and/or TNFα) while no response is found for cells secreting Th2 cytokines (IL-4, IL5, IL-13). IgG serotypes, predominantly IgG1 and IgG3, are also consistent with a Th1-polarised response, which is the profile targeted for COVID-19 vaccine in order to avoid potential disease enhancement.

Finally, although AZD1222 elicits the development of neutralising antibodies against the viral vector, they do not seem to interfere significantly with the magnitude of the anti-spike response.

Clinical efficacy

Based on the description of the study population presented with the interim analysis, the study results are considered to support vaccine efficacy in a population at risk of severe COVID-19 based on comorbidities. There is some uncertainty about the effects of the vaccine in subjects over 65 years of age as this population is currently not well represented. As good efficacy has been demonstrated in subjects with comorbidities and immunogenicity results in the elderly population are broadly comparable to those of younger adults, there is currently no indication of a significant loss of efficacy in this population.

Overall, the current data show a high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is slightly longer than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived.

However, the data do not address the following aspects.

- Data are currently limited for dose intervals < 2 months. However, more data on 4 to 6 week-intervals will be submitted with further analyses of the ongoing trials. Therefore, a pragmatic approach allowing for some degree of flexibility in dosing intervals is currently considered appropriate within the context.

- Data on severe disease are insufficient to draw any definite conclusion although no case has been reported in the AZD1222 group and the vaccine efficacy has been shown on hospitalisations occurring after the first dose.

- Although data in individuals above 65 year of age are currently limited, more information is expected in the near future, with the submission of further analyses of the ongoing trials.

- Regarding COVID-19 cases, no viral genomic sequencing data of the isolated strains and no immunogenicity data in these vaccine failures are currently available. This will be addressed at a broader level by the COVID-19 Genomics UK (COG-UK) Consortium and in the immunogenicity follow-up.

- There are no data in pregnant women and immunosuppressed patients as these subjects are excluded from the trial. These aspects are addressed in the Risk Management Plan.

- Data on vaccine protection after 2 doses are currently lacking beyond 2-3 months and this will be addressed with longer follow-up in the ongoing clinical trials and effectiveness studies in accordance with the Risk Management Plan.

- There are currently no data in adolescents (12 to 17 years old). Enrolment in a safety and immunogenicity sub-study is due to start and these data will be submitted when available.

Clinical Safety

As of the 04 November 2020 data cut-off, safety data were available for 23,745 subjects. Of these subjects, 12021 subjects received at least one dose of AZD1222 of which 8266 received 2 doses of AZD1222. The median duration of follow-up post dose 2 was 62 days in the AZD1222 and control groups, which is acceptable in the context of this Regulation 174 procedure.

The safety profile is characterised by local and systemic reactogenicity, which is likely to affect most recipients to a mild or moderate degree for a few days after vaccination. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. No major safety concerns are raised. Based on the solicited local and systemic reactogenicity data, and the adverse event data, the following adverse drug reactions have been included in the Information for Healthcare Professionals and the Information for UK recipients:

- Very common (≥ 10%): headache, nausea, myalgia, arthralgia, Injection site tenderness, injection site pain, injection site warmth, injection site erythema, injection site pruritus, injection site swelling, injection site bruising (including injection site haematoma – uncommon), fatigue, malaise, pyrexia (including feverishness – very common, and fever ≥ 38° - common), chills

- Common (≥ 1% to < 10%): vomiting, injection site induration, influenza-like illness

- Uncommon (≥ 0.1% to < 1%): lymphadenopathy, decreased appetite, dizziness, abdominal pain, hyperhidrosis, pruritus, rash

A very small number of neuroinflammatory events have been reported following vaccination with AZD1222 but a causal relationship with AZD1222 has not been established. 'Neuroinflammatory conditions' is included in the RMP as an important potential risk and will be closely monitored by routine and additional pharmacovigilance activities.

Analyses of safety data by age, comorbidity (yes/no), baseline SARS-CoV-2 status and country have been provided. These analyses do not raise any specific concerns.

In the AZD1222 group, only 18% of subjects were >55 years of age and about 10% were ≥ 65 years of age. Whilst data are therefore limited in older subjects, particularly those ≥ 65 years, it is of reassurance that the frequency and severity of solicited adverse events was lower in subjects ≥ 65 years, and the incidence of serious adverse events and adverse events of special interest was similar between subjects less than and ≥ 65 years. In addition, no clinically relevant difference was seen in the larger population of subjects that had at least one comorbidity. Therefore, it is considered that the available evidence supports a broad indication.

Whilst the number of subjects with severe COVID-19 is too low to assess the potential for vaccine-associated enhanced disease, the type of immune response triggered by the vaccine (Th1 skewed) and a review of the number of COVID-19 hospitalisations in the 2 treatment groups provides reassurance (2 vs 16) regarding this theoretical risk. As VAED may not become apparent until efficacy of the vaccine starts to wane this is included as an important potential risk in the RMP with both routine and additional pharmacovigilance activities planned.

There are no data in pregnant or breastfeeding women or immunosuppressed subjects. These populations are identified as missing information in the RMP with both routine and additional pharmacovigilance activities planned.

The safety population, exposure and length of follow-up are acceptable for authorisation for temporary supply under Regulation 174. Safety data corresponding to longer follow-up will be submitted as laid out in the RMP.

Conclusion on the clinical aspects

The short-term data for COVID-19 Vaccine AstraZeneca are supportive of a favourable benefit/risk. From a clinical perspective, based on the reviewed information, there is no objection to the temporary supply of COVID-19 Vaccine AstraZeneca under a Regulation 174.

V USER CONSULTATION

Evaluation of the patient information for readability via a user consultation study is currently deferred in the context of emergency supply under a Regulation 174.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable in the context of batch specific release under Regulation 174. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 18 years of age and older.

The use of COVID-19 Vaccine AstraZeneca should be in accordance with official guidance.

The Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca and the Information for UK recipients on COVID-19 Vaccine AstraZeneca are satisfactory.

The Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca and the Information for UK recipients on COVID-19 Vaccine AstraZeneca for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**