



1. Home (<https://www.gov.uk/>)
  2. Health and social care (<https://www.gov.uk/health-and-social-care/>)
  3. Medicines, medical devices (<https://www.gov.uk/health-and-social-care/medicines-medical-devices-blood/>)
  4. Pharmacy (<https://www.gov.uk/health-and-social-care/pharmacy/>)
  5. Regulatory approval of COVID-19 Vaccine AstraZeneca (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/>)
- Medicines & Healthcare products Regulatory Agency (<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/>)

Decision

# Summary of the Public Assessment Report for AstraZeneca COVID-19 vaccine

Updated 6 January 2021

## Contents

Summary of the Public Assessment Report

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

1. Introduction
2. Quality aspects
3. Non-clinical aspects

Further information

[Print this page](#)



© Crown copyright 2021

This publication is licensed under the terms of the Open Government Licence v3.0 except where otherwise stated. To view this licence, visit [nationalarchives.gov.uk/doc/open-government-licence/version/3](https://www.nationalarchives.gov.uk/doc/open-government-licence/version/3) (<https://www.nationalarchives.gov.uk/doc/open-government-licence/version/3>) or write to the Information Policy Team, The National Archives, Kew, London TW9 4DU, or email: [psi@nationalarchives.gov.uk](mailto:psi@nationalarchives.gov.uk).

Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned.

This publication is available at <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/summary-of-the-public-assessment-report-for-astrazeneca-covid-19-vaccine>

## Summary of the 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 (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/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 (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-uk-recipients-on-covid-19-vaccine-astrazeneca>) and Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/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 COVID19 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 (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-uk-recipients-on-covid-19-vaccine-astrazeneca>) or the Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/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.

### 1. 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  $\geq 18$  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 (<https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/conditions-of-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.

## 2. Quality aspects

### 2.1 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)  $5 \times 10^{10}$  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.

### 2.2 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.

## **2.3 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 inprocess 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. The 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 (**GMQ**). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant.

## 2.4 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.

## 3. Non-clinical aspects

### 3.1 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 intramuscular 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 COVID19 Vaccine AstraZeneca is sometimes referred to as AZD1222.

## 3.2 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 108 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 CoV2 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.

### 3.3 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  $3 \times 10^8$  to  $9.97 \times 10^9$  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.

## 3.4 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  $3.7 \times 10^{10}$ ) 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  $3.7 \times 10^{10}$ ) 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  $1 \times 10^{10}$  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 embryofetal 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  $2.59 \times 10^{10}$  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  $2.59 \times 10^{10}$  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  $2.59 \times 10^{10}$  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  $1.7 \times 10^{10}$  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)  $5 \times 10^{10}$  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.

### 3.5 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.

### 3.6 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.

### Further information

The rest of this document, including sections on clinical aspects, user consultation, and the overall conclusion, can be found in the PDF

([https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/949772/UKP\\_AR\\_COVID\\_19\\_Vaccine\\_AstraZeneca\\_05.01.2021.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949772/UKP_AR_COVID_19_Vaccine_AstraZeneca_05.01.2021.pdf)).

Print this page