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Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: ChAdOx1-S

Product name: ChAdOx1 CoV-19

Sponsor: Astra Zeneca

Submission number: PM-2020-06115-1-2

eSubmission number: e005766

evaluator: [redacted]

Date of report: 27th January 2020

TRIM reference: D21-2111228

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TGA Health Safety Regulation

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- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

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List of abbreviations

Abbreviation	Meaning
AZD 1222	COVID 19 vaccine Astra Zeneca (COVID-Vaccine (ChAdOx1-S) Also known as ChAdOx1 nCoV-19
AdHu5	Human adenovirus 5
CCR7	CC chemokine receptor 7
CD	Cluster of differentiation
ChAd63	Chimpanzee adenovirus 63
ChAdOx1	Chimpanzee adenovirus ox 1
ChAdOx1MERS	Chimpanzee adenovirus ox1 with MERS spike antigen
ChAdOx2	Chimpanzee adenovirus ox2
DP	Drug product
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunospot
GMFR	Geometric fold rise
GMR	Geometric means response
GMT	Geometric mean titre
HAdV-4	Human adenovirus 4
ICS	Intracellular cytokine signalling
IFNλ	Interferon gamma
IL	interleukin
LD	Low dose
M1	Influenza A matrix protein 1
MenACWY	Meningococcal group a,c, w-135 and y conjugate vaccine
MERS-COV	Middle eastern respiratory coronavirus
ME-TRAP	Multiple epitopes and thrombospondin related adhesion protein
MNA	Microneutralisation assay

Abbreviation	Meaning
nAb	Neutralising antibodies
NP	Influenza a nucleoprotein
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PRNT	Plaque reduction neutralisation test
qPCR	Quantitative polymerase chain reaction
RBD	Receptor binding domain
RT-PCR	Reverse transcriptase PCR
SD	Standard dose
SFC	Spot forming cell
Th	T helper
TNFα	Tumour necrosis factor alpha
VAED	Vaccine associated enhanced disease
vp	Viral particle
v/v	Volume per volume
w/v	Weight per volume

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1. Submission details

1.1. Identifying information

Submission number	PM-2020-06115-1-2
eSubmission number	e005766
eSubmission sequences covered in this report	0000 to 00005
Sponsor	Astra Zeneca
Trade name	COVID-19 Astra Zeneca
Active substance	ChAdOx1-S

1.2. Submission type

This was a type A application for provisional registration for a new vaccine for the treatment of SARS-CoV-2.

1.3. Drug class and therapeutic indication

The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2, with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for the spike protein.

Proposed Indication (as of 7th December 2020)
COVID-19 Vaccine AstraZeneca is indicated for active immunisation of individuals ≥ 18 years for the prevention of coronavirus disease 2019 (COVID-19)

1.4. Dosage forms and strengths

The formulation is a multidose vial containing 1 X 10^{11} vp/ml. Each dose is prepared by withdrawing 0.5ml from a vial.

1.5. Dosage and administration

Two doses of 5 X 10^{10} vp (nominal) at an interval of 4-12 weeks.

1.6. Formulation

1.6.1. Formulation development

Previous clinical trials for a ChAdOx1 vectored vaccine have included those for influenza (fusion protein NP + M1), tuberculosis, prostate cancer, malaria, chikungunya, Zika, MERS-CoV and meningitis. None of these vaccinations are registered for clinical use.

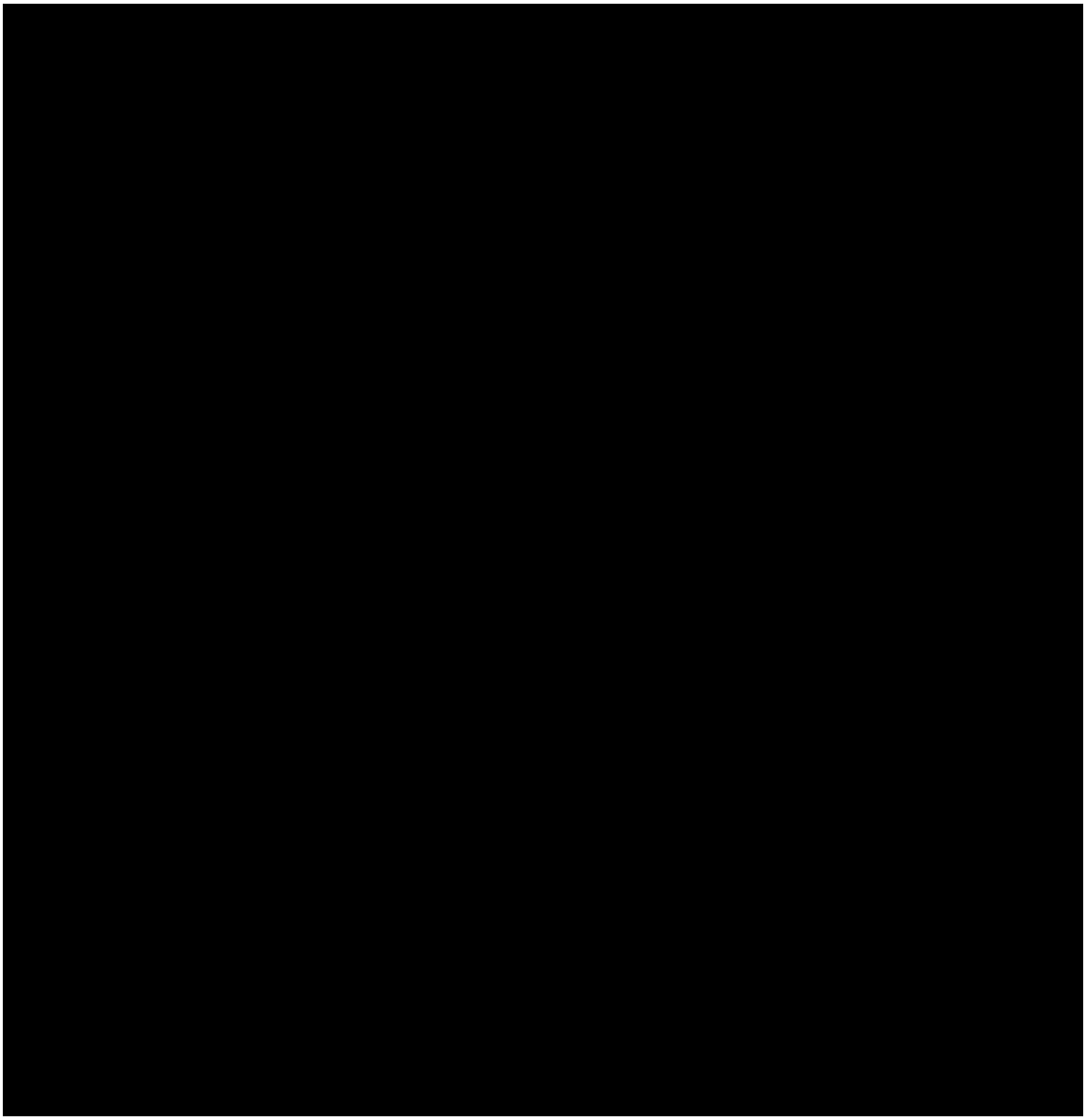
The aim of the formulation development was to enable frozen storage of the drug substance and storage the drug product at 2-8 degrees for at least 6 months. The manufacturing process for the drug substance and drug product have changed during the development of this product. The

manufacturers in the clinical trials included Clinical Biomanufacturing Facility at the University of Oxford (process 1), Advent (process 2) and Cobra/Symbiosis (process 3).

There are additional changes in the manufacturing process planned for commercial scale batches (process 4). The sponsor has developed a comparability plan to assess the similarity of the drug substance and product between these manufacturing processes (see Table 1).

Evaluator comment: The quality and manufacturing group will be asked to comment on the appropriateness of these processes in their reports.

Table 1: AZD1222 comparability plan (from table 11 drug substance overview and table 9 drug product overview In Module 2)



[redacted]

Chimpanzee adenoviral vectors:

A chimpanzee adenovirus vector was used to avoid the problem of pre-existing immunity to human adenovirus. Chimpanzee adenoviruses are not known to cause pathological illness in humans.

The prevalence of antibodies to chimpanzee origin adenoviruses in people living in the US is small, but increases in other countries.

Development of the AZD 1222 drug substance

AZD 1222 is produced using HEK293 cells from virus seed made by reverse genetics and purified using chromatography and tangential flow filtration.

The ChAdOx1 vector is derived from chimpanzee adenovirus Y25. The E1 gene has been deleted making it replication deficient (unable to replicate in human cells). The E3 gene (an immunomodulatory protein that would normally suppress the immune response) has also been delete to improve immunogenicity. Further modifications to the E4 open reading frame have been made to improve manufacturing yield.

[redacted]

[redacted]

1.6.2. Excipients

The vaccine is preservative free.

Excipients include 10mM histidine/histidine hydrochloride, 35mM sodium chloride, 1mM magnesium chloride hexahydrate, 0.1mM disodium edetate, 7.5% w/v sucrose, 0.5% v/v ethanol absolute, 0.1% w/v polysorbate 80.

Histidine and histidine hydrochloride are set at a ratio appropriate for buffering the Drug Product at a target pH of 6.6. Sodium chloride is used as a cryo-protectant to stabilise the virus during freeze/thaw and then act as a tonicity agent for parenteral dosing. Magnesium is used as a cation to stabilise the virus by electrostatic interactions. Disodium edetate and ethanol are used to stabilise the virus by preventing free radical induced oxidation of the virus. Sucrose is used as a cryo-protectant to stabilize the virus during freeze/thaw and enhance thermal stability. Polysorbate 80 is used as a surfactant to stabilize the virus by reducing virus adsorption to surfaces and minimizing interactions at air-liquid interfaces.

Evaluator note: A number of cases of anaphylaxis have been reported since the Pfizer mRNA vaccine has been registered and rolled out in Europe and the USA. It is thought that the excipient PEG may be the cause of that. Polysorbate 80 is of the same chemical class of PEG, and it is possible that a similar risk of anaphylaxis may arise from the AZ vaccine. However many other vaccines used in Australia also contain polysorbate 80.

1.7. Regulatory history

1.7.1. Australian regulatory history

A pre-submission meeting with the TGA was held on the 16th September 2020. Various other meetings were held with specific sections in relation to quality, batch release, pharmacovigilance, and GMP.

The sponsor submitted an application for provisional determination on the 4th October. This was granted on the 9th October.

Data was received by a rolling submission, initially via email then in eCTD format. In addition, the sponsor made evaluation reports and questions from other international regulators available to the evaluator. The sponsor was very accommodating to TGA questions.

The vaccine contains a genetically modified organism. A concurrent application is being assessed by the Office of the Gene Technology regulator for a dealing involved with the intentional release of a genetically modified organism.

Note: Emergency Use Authorisation was not considered for the COVID-19 vaccines in Australia.

1.7.2. Orphan drug designation

Not relevant.

1.7.3. Related submissions

Nil

1.7.4. Overseas regulatory history

There has been no application to the FDA.

A submission with the UK MHRA and EMA was lodged on 30 September 2020. On the 30th December, the MHRA granted emergency use authorisation to the vaccine. The CHMP are meeting to discuss this vaccine the week beginning 25th January.

A submission with Singapore, Canada and Switzerland was lodged in October 2020.

1.8. Guidance

1. FDA: Development and Licensure of vaccines to prevent COVID-19. Guidance for Industry. June 2020
2. WHO: Design of vaccine efficacy trials to be used during public health emergencies-points of consideration and key principles.
3. EMA. EMA considerations on COVID-19 vaccine approval. 16th November 2020.

Note: The FDA and EMA describe an efficacy of over 50% with lower 95% confidence interval of > 30% as sufficient for registration purposes. The EMA recommends the primary efficacy endpoint be in the seronegative population, whereas the FDA recommend the primary efficacy endpoint not be restricted to those that are seronegative as screening is unlikely to be performed prior to vaccination.

From WHO guidelines: The major goal of conducting clinical efficacy studies during PHEs is to obtain data that can support broader use of a vaccine under a defined regulatory framework. It is recognized that some of the relevant data may be collected either before or after the PHE, but it is presumed that efficacy data from a study conducted at a time when disease transmission is ongoing is central for regulatory approval. Because of the confidence that product licensure provides in safety and effectiveness, licensure, with or with a requirement for post-licensure confirmation of product effectiveness, is normally the ultimate goal. Thus, clinical studies are typically aimed at accumulating data that will support this end result.
These data could also support other uses of the vaccine in the interim between trial completion and licensure, including temporary approval through "expanded access" use, Emergency Use Authorization (EUA), or a similar mechanism. This special procedure gives time-limited approval to a product for a disease in a PHEIC. Use of the vaccine must have oversight by a functional national regulatory authority (NRA) in conjunction with the WHO Emergency use assessment and listing (EUAL) for vaccines. EUA/EUAL normally does not require consent, though consent requirements should be considered in conjunction with the data that will be submitted to/reviewed by regulators. EUA determination reflects a lower level of certainty about the effectiveness of the product as compared to licensure. While the degree to which product safety and effectiveness has been established may differ among these various regulatory mechanisms, they all share the need for scientifically valid data that supports product effectiveness. It should be recognized that widespread distribution of a vaccine prior to obtaining sufficient data to support licensure will likely interfere with collecting that data, and may lead to a situation in which licensure is significantly delayed.

During the regulatory decision-making process, clinical trial results will be evaluated by regulators based on principles not only of good clinical practice, but also of good trial design. This includes evaluation of potential biases, speaking to the importance of measures like randomization and blinding that can reduce potential biases in clinical trial outcomes. Previous consultations have concluded that it may be ethical to conduct randomized trials under circumstances when there are insufficient data to support widespread use or licensure of a product ..Selection of the primary endpoint for vaccine efficacy trials in PHEs is usually guided by the desired indication for use, taking into account considerations of study power.

Consideration in setting success criteria may include product safety and benefit, the public health need (including incidence and severity of the disease), the availability of other products, and the totality of available data on the product

1.9. Evaluator's commentary on the background information

The background information was adequate.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

This was a rolling submission.

The first clinical package was received on the 7th December 2020. It contained key tables from participant disposition, demographics, baseline characteristics, efficacy and safety.

A second clinical package was received on the 10th December. This was described as containing the main efficacy analysis with complete efficacy and safety results from the pooled population. However, the report did not provide much more helpful information from the previous data package.

A third clinical package containing updates from minor errors from previous clinical packages, and further information about subgroups including country, co-morbidity, age and serological status at baseline was provided.

The fourth clinical package contained a clinical overview, PI, CMI, sponsor's responses to EMA's clinical questions. Subsequent updates have included responses to questions from other regulators.

The fifth clinical package was received on the 16th January. This consisted of a summary of biopharmaceutical studies and associated analytical methods, summary of clinical pharmacology studies, summary of clinical efficacy, summary of clinical safety, and literature references.

The sponsor has regularly provided updates to the TGA with questions and answers from other regulators, including the MHRA PARS and EMA evaluation questions.

2.2. Paediatric data

All of the studies in the interim analysis were performed in adults aged 18 years and older. Study CV002 plans to recruit a small number of paediatric patients.

It is our understanding that approval of the vaccine in paediatrics will be the subject of a future submission. The sponsor will be asked to describe the clinical development program proposed to justify use in paediatrics.

2.3. Good clinical practice

In each clinical study protocol, it is stated that ' the investigators will ensure that this study is conducted according to the principles of the current version of the Declaration of Helsinki' and that 'the investigator will ensure that this trial is conducted in accordance with relevant regulations and with good clinical practice'.

2.4. Evaluator's commentary on the clinical dossier

The dossier was received as a rolling a submission. Data was initially received via email, then subsequently in eCTD format. Initially, it was unclear where in the data package information

was and the evaluation took some time. The sponsor was very accommodating for requests for information, and in sharing questions and responses from other international regulators.

The evaluator used additional literature references to support the data on immunology that was available in the clinical studies.

There was very little information about an ongoing clinical study in the USA. This is a Phase III randomised, double blind, placebo controlled study of AZD1222 for the prevention of COVID-19 in adults. The study commenced on 28 August and is expected to be completed in February 2023, with an interim analysis in January 2021. The estimated enrolment is 40 000 participants. Of these, 25% will be over 65 years. The study is examining only the standard dose (5X 10^{10}vp/ml) given 28 days apart. The interim analysis of this study will be available in March 2021.

3. Pharmacokinetics

Studies in mice have shown that the ChAdOx1 vector is distributed at low levels into a range of tissues including spleen, brain, heart, kidney, liver, lung, lymph nodes, testes, ovary.

There was a very low level of viral shedding on the skin at the site of injection in humans given another vaccine using the ChAdOx platform (AdCh63 ME-TRAP). No viral shedding was detected in urine or faeces.

No vector shedding studies were performed for ChAdOx1-S COVID-19.

3.1. Studies providing pharmacokinetic information

No clinical studies submitted.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic information

Immunological data was obtained from clinical studies COV001, COV002, COV003, and COV005. In addition, the evaluator has included data from published studies described in section 19.

4.2. Summary of pharmacodynamics

4.2.1. Mechanism of action

AZD 1222 is a monovalent vaccine composed of a single recombinant, chimpanzee adenovirus vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein is expressed locally and stimulates a humoral and cellular immune response.

The ChAdOx1 viral vector is replication deficient as the essential E1 gene region has been deleted. It is unable to replicate within vaccinated animals or humans.

A second dose of AZD 1222 increases both the magnitude and avidity of antigen specific IgG generated. These S-specific antibodies are polarised towards the production of IgG1/IgG3.

AZD 1222 induces CD8-T cells which are responsible for destroying virus infected cells, and preventing the spread of the virus after infection; in addition the Th1 response which supports B cell function for the production of antibodies.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects including timecourse

After the first dose of vaccine, immunoglobulin levels against RBD and spike protein increased and peaked at day 28. If no further dose is given, antibody levels plateau. If a booster dose is given, there was a further increase in antibody titre which peaked at day 42 (see section 13.1.1, Table 24,Table 25, Table 26).

IFN-λ ELISpot responses peak day 14 after vaccination with no further increase with a booster dose (Table 29). Intracellular cytokine staining on 70 participants in COV001 and COV002 showed induction of Th1 cytokines (IFN λ, IL-2 and TNF α) and CD4 populations with polyfunctionality. There was no induction of Th2 cytokines.

There was no information of antibody response after 56 days of the second vaccination dose in either the published studies or clinical studies.

4.2.2.2. Secondary pharmacodynamic effects including timecourse

Anti-ChAdOx1 (anti-vector) neutralising antibodies increase with the prime vaccination and peak at day 28. There is no further increase after a booster dose (see figure 7 section 13.1.1). The sponsor has stated that these anti bodies do not appear to influence the antibodies generated to RBD or spike protein.

4.2.3. Relationship between drug concentration and pharmacodynamic effects

After the first dose of vaccine, the LD vaccine produced a lower antibody response than the SD vaccine. However after the second dose, those who received the initial LD had a greater antibody response after the second standard dose than patients who received two SD vaccine (Table 24).

4.2.4. Genetic, gender and age related differences in pharmacodynamic response

In a study by Ramasay (section 19.1.1), similar antibody and T cell responses were seen in participants aged 18-55years, 56-69 years and > 70 years. However, in the clinical studies the antibody response in patients over 65 years was around two thirds of that seen in patients less than 65 years (Table 28). This was attributable to a shorter dose interval.

ELISpot data suggests similar IFN λ and T cell response in the elderly is similar to the younger population (Table 29).

There was no significant difference in antibody titre in different genders or racial groups.

4.2.5. Pharmacodynamic interactions

Not examined

4.3. Evaluator's overall conclusions on pharmacodynamics

Although there are no defined immune correlates of protection against COVID-19, it is generally considered that high titre neutralising antibody titres with a robust cytotoxic T-cell response and Th1 biased CD+4 effector response will be optimal for protective immunity. Strong Th1 skewed T cell responses can drive protective humoral and cell mediated immune responses and might reduce the potential for disease enhancement.

AZD1222 induced both humoral and Th1 response. After the first dose of SD, the antibody levels were similar to that seen in convalescent plasma. If no booster dose is given, they remain stable after day 28. Anti-ChAdOx1 antibodies are induced after the first dose, are in low levels, and

seem to remain stable up to at least 56 days. A booster dose leads to an increased antibody response but not T-cell response.

In the clinical studies, antibody levels after the second dose tended to increase as the duration between first and second dose increases. The reason scientific reason for this is unclear.

There is a general concern about immunosenescence. In the Phase II part of COV002, the level of antibody response in the elderly (≥ 70 years) is comparable to that of younger age groups. These data differ from those of the Phase III part where the antibody response in the elderly was less, however this is confounded by a broader population including subjects with comorbidities and a shorter dose interval in the elderly. In addition, different antibody assays were used in the different studies.

The duration of immunity after a single or repeat doses is unknown.

5. Dosage selection for the pivotal studies

5.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The dose of 5 X 10^{10}vp used for the early clinical studies was based the dose found to elicit an antibody response in another ChAdOx1-vectored vaccine study for MERS-CoV. The sponsor has stated that dose regimen of an initial dose then repeat dose after 4-12 weeks was based upon accumulated evidence from animals and other ChAd vector vaccines.

However, the initial study protocols CV001, CV002 and CV003 and CV005 were for a single dose. A second dose was included as a protocol amendment following results of the subgroup analysis of COV-001 which showed better antibody responses in those who had a second dose.

An initial low dose was part of the planned protocol of study COV-002, and arose in another

[redacted]

Evaluator comments:

The strategy for finding the optimal dose and dosing interval was not ideal, and has led to considerable uncertainty about the optimal dosing regimen.

The immunological correlates for immunity to COVID-19 have not yet been established. Thus, although use of a repeat dose regimen to optimise the immune response is scientifically plausible, it is not clear what level of antibody response is protective and if sufficient antibody response is achieved after the first dose. .

The inadvertent administration of a lower dose of vaccine and variable times between doses could be seen as protocol violations. Generally, these subjects are eliminated from per protocol analysis. Any results generated under these conditions needs to be viewed with caution as there were no pre-planned statistical methods to deal with the protocol violations, there are many confounding factors, and the studies were not powered for the results.

6. Clinical efficacy

The data in support of clinical efficacy is based upon an interim meta-analysis of 4 ongoing clinical studies (COV001, COV002, COV003, COV005). The interim analysis was performed to enable the use of the vaccine under EUA or conditional approval while awaiting the full data.

6.1. Studies providing evaluable efficacy data

Table 3: Key design elements for the AZD1222 clinical studies contributing to the pooled analysis

Element	COV001	COV002	COV003	COV005
Phase	I/II	II/III	III	I/II
Region	United Kingdom	United Kingdom	Brazil	South Africa
Study population	Healthy adults, aged 18-55 years	Main efficacy study: Adults, aged ≥ 18 years	Health professionals and adults with high potential for exposure to SARS-CoV-2, aged ≥ 18 years	Adults, aged 18-65 years
Number of doses (IM route)	One or two (based on study group)	One or two (based on study group)	Two	Two
AZD1222 dose levels	SD: 5×10^{10} vp LD: 2.5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp
Control	MenACWY	MenACWY	MenACWY (first dose) Saline (placebo; second dose)	Saline (placebo)

HD = high dose; HIV = human immunodeficiency virus; IM = intramuscular; LD = low dose; MenACWY = meningococcal Group A, C, W-135 and Y conjugate vaccine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vp = viral particle.

These studies have a similar designs, however have some differences including

- Country – risk of COVID due to epidemiology at that time, different health care systems,
- Number of doses- many participants in COV001 had only one dose due to the study starting enrolment before the protocol change
- Dose quantity- LD versus SD

- Source of vaccine (ie manufacturing site)
- Different control
- Age – due to changes in the age of participants as experience with the vaccine in the trial increased

Inclusion and exclusion criteria are described in section 13.3.1. It is important to note that patients with significant co-morbidities were excluded from the clinical studies.

Evaluator comment: In any analysis of the results, it is important to be aware of this heterogeneity. Although subgroup analysis will be performed, this may be limited by the small numbers and other confounding factors.

6.2. Pivotal or main efficacy studies

6.3. Analyses performed across trials: pooled and meta analyses interim analysis

For this interim analysis, efficacy data contains pooled data from studies COV002 and COV003. Study COV 001 and COV005 were not included in the efficacy analysis as the number of cases was < 5. Data for safety was obtained from studies COV001, COV002, COV003 and COV005.

The cut off date for the pooled efficacy analysis was 4th November 2020. This was based upon having obtained the pre-determined number of cases for an interim analysis.

6.3.1. Objectives:

The primary objective of the pooled analysis were to: estimate the efficacy of two IM doses of AZD1222 with the second dose being SD, compared to control for the prevention of COVID-19 in adults > 19 years of age.

Secondary objectives of the pooled analysis were to

1. Evaluate the efficacy of AZD 1222 against severe disease
2. Assess the safety, tolerability and reactogenicity of AZD 1222
3. Assess the humeral immunogenicity of AZD 1222
4. Assess the cellular immunogenicity of AZD 1222

6.3.2. Statistical analysis

[redacted]

Pooling of data was considered acceptable by the sponsor for the following reasons:
Studies COV001, COV002, COV003, and COV005 are all randomised, controlled studies in healthy volunteers with similar efficacy endpoints. Case detection methods for efficacy assessments are also similar. Access to care for passive case detection was available in all studies; COV002 also includes weekly self-swabs for detection of infection and COV005 includes nasal swab and/or saliva on each scheduled visit. Key inclusion criteria are similar for all studies, except for age. Study populations are generally similar. All studies excluded patients with serious conditions or receiving medication that could interfere with the study conduct or the interpretation of study data

One interim analysis of data and one final analysis of data was planned. The interim analysis was triggered when 53 COVID-19 cases (SARS-CoV-2 virologically confirmed) that occurred ≥ 15 days post the second dose have been reported in participants who received SDSD across the AZD1222 and control groups in pooled studies. This would provide 77% power for the 20% threshold to assume a true vaccine efficacy of 70%.

Evaluator note: the sponsor has stated that assuming a true VE of 60%, 105 cases gives 77% power to reject the null hypothesis that VE =30%.

Gamma Alpha-Spending function is used to control the overall Type 1 Error at 5%. The planned alpha level was 1.13% for interim analysis and 4.44% for primary analysis. The minimum observed VE if an interim or primary analysis demonstrates evidence of efficacy is 64% and 48%, respectively.

Vaccine efficacy (VE), which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group expressed as a percentage, will be calculated as VE = 1- relative risk. The VE, and its corresponding 2-sided (1-α) % confidence interval (CI), will be estimated from the model. In addition, the 2-sided p-value testing the null hypothesis that the incidence of SARS-CoV-2 virologically-confirmed primary symptomatic COVID-19 between AZD1222 and control groups are the same will be obtained from the model. The p-values are calculated for the test of any difference between test vaccine and control ie a statistically significant p value would reflect a VE > 0%. Therefore, confidence intervals are more relevant when assessing whether the vaccine meets the criteria determines by WHO.

For vaccine efficacy, the confidence interval and p value were estimated based on Poisson regression with robust variance including the terms study code, treatment, age group at screening as covariates, and the log of follow up time as an offset. For endpoints with rare events, the exact conditioning method for stratified Poisson regressing using PROC GENMOD with exact statement was used, as well as descriptive analysis.

For further information about the individual study designs, see the descriptions in sections 6.2.1, 6.2.2, 6.2.3 and 6.2.4.

The case definitions for efficacy were as follows:

Table 4 Case definitions for evaluation of efficacy

Case	Definition
COVID-19 (Primary) Virologically-confirmed[a] symptomatic cases of COVID-19	PCR-confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.
COVID-19 Severe Disease	WHO grade ≥ 6[b]
COVID-19 Hospital Admission	WHO grade ≥ 4[b]
COVID-19 Requiring ICU	WHO grade ≥ 7[b]

PCR testing

In study COV002- PCR swabs were performed weekly for asymptomatic cases, and as needed for symptomatic cases. In COV003, testing was performed for symptomatic cases only.

[redacted]

As of 7th December 2020, 76% of all expected swabs were returned with 95% of participants returning at least one swab.

6.3.3. Analysis populations

The following groups were excluded from the meta-analysis: groups without randomisation (group 3 of COV001, group 1 of COV002; participants previously vaccinated with a ChAdOx1 vectored vaccine (group 11 of COV002), participants with HIV diagnosed at study start (group 3 of COV005 and group 12 of COV0022), children < 18 years.

Analysis was performed for treatment received.

Table 5: Populations used in analysis

Population	Description
All participants analysis set	All participants screened for the studies, to be used for reporting disposition and screening failures.
Any Dose for Safety	All randomized adult participants who received at least 1 dose of study intervention (AZD1222 or control). Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. Erroneously-treated participants (e.g., those randomized to treatment A but are actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who received at least one dose of AZD1222 is classified as AZD1222. This analysis set will be used for safety analysis.
Any Dose for Efficacy	All participants in Any Dose for Safety but for groups in COV002, only efficacy groups (i.e., groups 4, 6, 9,10) will be considered. This analysis set will be used for efficacy analysis.
Dose1 SD for Safety	Only participants who received SD as the first dose of AZD1222 or in corresponding control group in Any Dose for Safety. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for safety analysis.
Dose1 SD Seronegative for Efficacy	Only participants seronegative at baseline in Any Dose for Safety who received SD as the first dose of AZD1222 or in corresponding control group, and remain on-study 22 days after their first dose without having had a prior SARS-CoV-2 virologically-confirmed COVID-19 infection.

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

Population	Description
	rule of Any Dose for Safety analysis set. This analysis set will be used for safety analysis.
LDSD Seronegative for Efficacy*	Only participants seronegative at baseline in SDSD + LDSD Seronegative for Efficacy analysis set who received LDSD or in the corresponding control group, and remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 virologically-confirmed COVID-19 infection. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for the efficacy analysis.
Dose1 LD Seronegative for Efficacy*	Only participants seronegative at baseline in Any Dose for Safety who received LD as the first dose of AZD1222 or in corresponding control group, and remain on-study 22 days after their first dose without having had a prior SARS-CoV-2 virologically-confirmed COVID-19 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9,10) will be considered. The treatment assignment will follow the same rule of Any Dose for Safety analysis set. This analysis set will be used for efficacy analysis.
LDSD for Immunogenicity*	Only participants in Any Dose for Safety who received LDSD of AZD1222 or in corresponding control group. Participants without at least one post baseline immunogenicity result will be excluded. The treatment assignment will follow the same rule of Any dose for safety analysis set. This analysis set will be used for immunogenicity analysis.
SDSD + LDSD for Immunogenicity	Only participants in Any dose for Safety who received LD/SD or SD/SD of AZD1222 or in corresponding control group. Participants without at least one post baseline immunogenicity result will be excluded. The treatment assignment will follow the same rule of Any dose for safety analysis set. This population will be used for the immunogenicity analysis.
SDSD for Immunogenicity	Only participants in Any Dose for Safety who received two SDs of AZD1222 or in corresponding control group. Participants without at least one post baseline immunogenicity result will be excluded.

Population	Description
	The treatment assignment will follow the same rule of Any dose for safety analysis set. This analysis set will be used for immunogenicity analysis.

* These populations were added after unblinding

Evaluator comment:

Ideally, primary efficacy analysis should include an ITT and a per protocol analysis. The sponsor has included a LDSD and SDSD seronegative ITT analysis who had been followed for 15 days after the second dose. Efficacy in the any dose for efficacy (which included single dose and 2 doses and variable follow up) may mimic success in the real world with variable compliance with dosing. The SDSD seronegative for efficacy group would be the closest group for a per-protocol analysis. The rationalefor combining the LDSD and SDSD set was to improve the power of the study, as the LDSD group was considered to have a similar efficacy in view of the similar antibody response.

Table 6: Description of the analysis populations for the meta-analysis

Analysis set	AZD1222	Control	Total
All participants randomized	12018	11735	23753
Any dose safety	12 021	11 724	23 745
Dose 1 SD for safety	10069	9902	19971
Dose 1 LD for safety	1947	1822	3769
Any dose efficacy	10014	10000	20014
SDSD + LDSD seronegative for efficacy	5807	5829	11636
SDSD seronegative for efficacy	4440	4455	8895
LDSD seronegative for efficacy	1367	1374	2741

The analysis populations are defined in the Statistical Analysis Plan, Section 6.
LD = low dose; SD = standard dose

6.3.3.1. Participant disposition:

As of the 4th November 2020, 23745 participants were enrolled and treated with at least dose of study intervention. The distribution of participants in different studies/sites included:

Study COV001, United Kingdom, 1067 or 4.5%
Study COV002, United Kingdom, 10663 or 44.9%
Study COV003, Brazil, 10002 or 42.1%
Study COV005, South Africa, 2013 or 8.5%

Table 7: Participant disposition of the meta-analysis. All participants (safety set)

	Number (%) of Participants		
	AZD1222	Control	Total
Participants in Any Dose for Safety Analysis Set	12021	11724	23745
Ongoing in study	11956 (99.5)	11656 (99.4)	23612 (99.4)
Completed study	0	0	0
Discontinued early from study	65 (0.5)	68 (0.6)	133 (0.6)
Reason for discontinuing early from study			
Adverse Event	0	1 (<0.1)	1 (<0.1)
Death	1 (<0.1)	4 (<0.1)	5 (<0.1)
Exclusion Criteria Met	1 (<0.1)	1 (<0.1)	2 (<0.1)
Lost To Follow-Up	8 (0.1)	11 (0.1)	19 (0.1)
Other	13 (0.1)	12 (0.1)	25 (0.1)
Physician Decision	0	1 (<0.1)	1 (<0.1)
Withdrawal By Subject	42 (0.3)	38 (0.3)	80 (0.3)

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

A high proportion of patients are included in the safety analysis set. However, the efficacy analysis set includes only 49% of the total number of participants. All of these are ongoing. No participants have completed the 12 month study. The main reason for the participants not being included in the efficacy analysis, is that they were dosed but did not receive the SDSD or LDSD regimen (3709). This included patients dosed with SD but follow up was < 15 days post dose, dosed with SD but developed COVID-19 within 15 days (AZ1222 25, control 41), dosed but did not receive SD as second dose (further detail in Table 52) .

Table 8: Participant disposition of the meta-analysis relevant to the efficacy analysis.

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

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

In the efficacy analysis, there were 5804 participants in the combined LD/SD and SDSD group, 4440 participants who received a SDSD regime, and 3450 participants who received a single SD.

Comment: The sponsor has described the combined LDSD + SDSD population as the main analysis set. The rationale was to provide greater power than just the SDSD population

Table 9: Exposure in the meta-analysis

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

[a] Dose level of control group is decided by the dose level of corresponding vaccine group.
Total row includes the number of participants with non-missing data for the corresponding characteristic and was used as the denominator for calculating percentages for all categories.
Source data: Main Safety Tables 1.2.1.1 and 1.2.1.2

6.3.3.2. Demographics

Age:

In the efficacy analysis set, 10218 (87.7%) were age 18-55 years, 10976 (94.3%) were 18-64 years, 444 (3.8%) were over 70 years. The oldest participant was 88 years.

BMI:

In the efficacy analysis set, the mean BMI was 26.43, range 11.4 to 95.6 kg/m2

Evaluator comment: The sponsor was ask to comment on the implausible BMI figures. They found a number of transcription errors which they plan to amend at the time of submitting the full clinical study results. .

Serostatus:

The initial protocol only included patients which were seronegative at baseline. Participants were enrolled regardless of serological state after a protocol change.

95.1% seronegative, 3% seropositive, 1.9% missing

See Table 51

Comorbidities:

Although 36% were noted to have co-morbidity, the number of serious co-morbidities was much lower. Serious co-morbidities were an exclusion factor. In the SDSD + LDSD seronegative analysis set, 1363 (11.7%) had respiratory disease, 270 (2.3%) had diabetes, 1817 (20.4%)

were obese, 508 (5.7%) had hypertension. See Table 50 for a detailed list of co-morbidities in the efficacy analysis.

6.3.4. Efficacy:

There were 131 events in COV002 and COV003. Of these 98 received the SD and 33 the LD as the initial dose

Note: Studies CV001 and CV005 were excluded from the efficacy analysis as there were < 5 cases in these studies. In study CV001, there was 1 case in the control group and 0 in the AZD1222 group. In study CV005, there were 2 cases in the control group and 0 in the AZD 1222 group.

Events were adjudicated by a central committee. The primary efficacy endpoint was the number of patients with symptomatic disease and positive COVID-19 PCR swab. The sponsor's primary efficacy population was those seronegative and received either the SDSD or LDSD.

PRIMARY EFFICACY

In the combined LDSD plus SDSD seronegative group, the vaccine efficacy was 70.42%, lower 95% confidence interval was 54.8%.

In the SDSD group, vaccine efficacy was around 62%. The lower 95% confidence interval was 40%,.

Thus, the vaccine efficacy in both populations was over 50% with the lower 95% confidence interval above 30%. This fulfils the EMA and FDA guidance criteria for an acceptable vaccine for COVID-19.

Table 10: Efficacy analysis for primary endpoint (included patients seronegative at baseline and received 2 doses and had more than 15 days follow up after the second dose)

Group	Cases/population AZD1222	Cases/population control	Vaccine efficacy and 95% CI	Median days follow up after the last dose for participants censored
SDSD and LDSD seronegative	30/5807	101/5829	70.42% (54.8-80.6)	48
SDSD and seronegative	27/4440	71/4455	62.1% (40-76.1)	36
LDSD and seronegative	3/1367	30/1374	90.1% (65.8-97.1)	56
All participants any dose	108/10015	227/10000	52.7% (40.5-62.4)	101

In the combined LDSD and SDSD seronegative group, the median duration of follow up 22 days after the first dose was 110 days (range 19-136) in the AZD 1222 group and 111 days (range 13-136) in the control group. The median duration of follow up 15 days after the second dose was 48 days (range 1-79) in the AZD 1222 group and the control group.

In the SDSD group, the median (range) duration of follow up 22 days after the first dose was 93 (19-127) in the vaccine group and 96 (13-27) in the control group. The duration of follow up 15 days after the second dose was 36 days (1-79) in the AZD122 group and 36 days (1-79) in the control group.

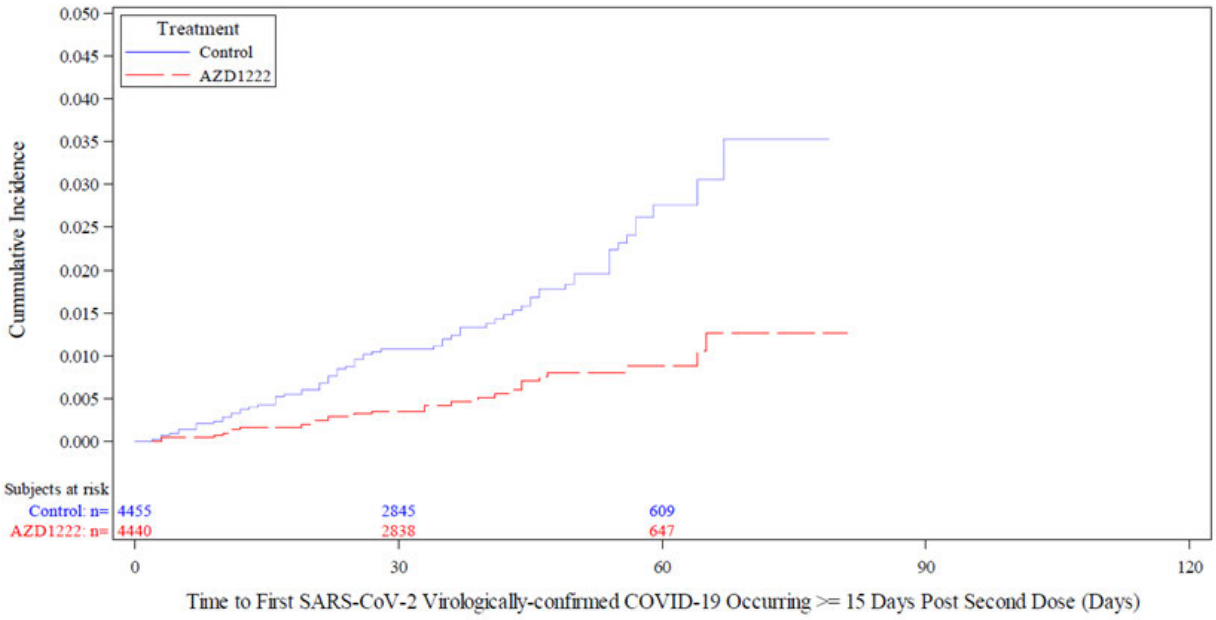
Efficacy was similar in UK and Brazil.

Table 11: Intention to treat analysis of vaccine efficacy for incidence of first SARS-CoV-2 virologically confirmed COVID-19 occurring more than 15 days post second dose using Poisson regression with robust variance by country

Study	Participants with events		VE (%)	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
COV002 (UK)	15 / 2380 (0.63)	38 / 2431 (1.56)	60.36	28.02, 78.18	0.002
COV003 (Brazil)	13 / 2067 (0.63)	32 / 2025 (1.58)	59.98	23.77, 78.99	0.005
Pooled (COV002 + COV003)	28 / 4447 (0.63)	70 / 4456 (1.57)	60.15	38.26, 74.28	< 0.001

Data cut-off date: 04 NOV 2020

Figure 2: Cumulative incidence plot for time to first SARS-Cov-2 virologically confirmed COVID-19 occurring more than 15 days post second dose of study intervention



The loss of participants with increasing time from 0 is noteworthy. Although there appears to be greater vaccine efficacy with increasing time since vaccination, this may be due to effects of lower number of patients in the denominator.

SECONDARY EFFICACY

The interim analysis was not powered for secondary or exploratory analysis. This is described here to see the trends only. There was a trend towards a reduction in the number of cases of severe disease and hospitalisation.

Table 12: Severe disease (WHO > 6) more than 15 days post second dose

	Cases/population AZD 1222	**Cases/population control**
SDSD and LDSD seronegative	0/5807	1/5829
SDSD seronegative	0/4440	0/4455

Table 13: Hospital admissions (> WHO grade 4)

	Cases/population AZD 1222	**Cases/population control**
SDSD and LDSD seronegative	0/5807	5/5829
SDSD seronegative	0/4440	4/4455
Any dose for efficacy	2/10014	16/10000

There were a similar number of asymptomatic cases in both groups. Interestingly, not an increased number as one would expect from a reduced number of symptomatic cases.

Table 14: Number of asymptomatic or unknown symptom cases of SARS CoV-2 in the SDSD+LDSD population who were seronegative at baseline

	Cases/population AZD 1222	**Cases/population control**
SD and LD seronegative	29/3744	40/3804

Note that swabs were only performed in study COV002. Approximately three quarters of participants returned all swabs. There may be some bias, in that patients who had symptom or exposure were more likely to return a swab. However this would affect both groups equally.

Efficacy of a single dose and dosing interval

Analysis of efficacy after a single dose was a secondary endpoint. Analysis of dosing interval was a post hoc subgroup analysis. Caution needs to be taken when interpreting this data due to the lack of statistical power in these numbers, and multitude of confounding factors.

Table 15 and Table 16 suggests that a single dose of SD vaccine offers protection of over 60% for 14 weeks between doses. A single dose of LD did not appear to be protective after 42 days.

However, it is important to note that there were very few infections in the control group at this time, attributed to a low number of cases in the community at that time.

Table 15: Number of cases per population of symptomatic COVID disease in seronegative patients after the first dose, before the second dose

Time since first dose	**SD**			**LD**		
	AZD	Control	VE	AZD	Control	VE
More than 22 days	51/6307	141/6297	64.07	12/1687	40/1686	70.15
More than 42 days	11/5202	29/5184	61.9 (23.9-80.6)	9/1683	8/1681	ns
More than 57 days	9/4860	23/4838	60.9 (15.7-81.8)	8/1678	8/1677	ns
More than 78 days	4/4179	12/4150	67.29 (-0.05-89.3)			

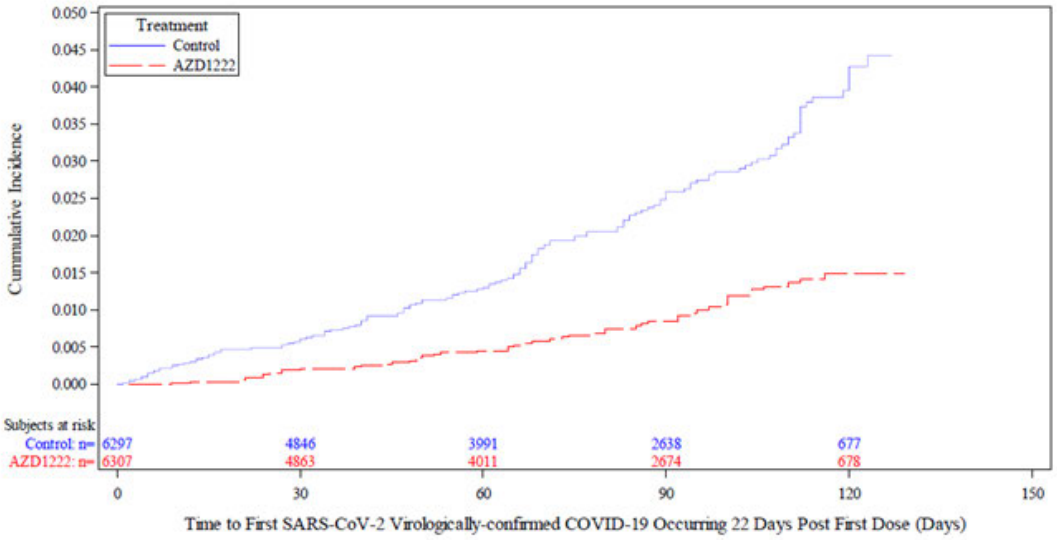


Figure 3: Cumulative incidence plot for time to first SARS-CoV-2 virologically confirmed COVID-19 occurring 22 days post first dose of study intervention

Table 16: Further breakdown of efficacy in the seronegative SD set by the time between dose 1 and dose 2

Pooled (COV002 + COV003)					
≥ 22 days post Dose 1 – Week 4	0 / 6307 (0)	11 / 6296 (0.17)	100	60.55, NE	<0.001
≥ 22 days post Dose 1 – Week 6	3 / 6307 (0.05)	23 / 6296 (0.37)	87.25	57.32, 96.19	<0.001
≥ 22 days post Dose 1 – Week 8	5 / 6307 (0.08)	29 / 6296 (0.46)	83.07	56.13, 93.47)	<0.001
≥ 22 days post Dose 1 – Week 10	9 / 6307 (0.14)	36 / 6296 (0.57)	75.26	48.50, 88.12	<0.001
≥ 22 days post Dose 1 – Week 12	10 / 6307 (0.16)	42 / 6296 (0.67)	76.38	52.86, 88.17	<0.001
≥ 22 days post Dose 1 – Week 14	11 / 6307 (0.17)	48 / 6296 (0.76)	77.19	56.03, 88.16	<0.001
≥ 22 days post Dose 1 – Dose 2	14 / 6307 (0.22)	52 / 6296 (0.83)	73.21	51.67, 85.15	<0.001

In the efficacy analysis, around 29% of subjects had a dose interval of < 6 weeks, 9% a dose interval 6-8 weeks, 25% a dose interval 9-11 weeks and 36% a dose interval > 12 weeks.

In post hoc analysis, there was a trend toward greater vaccine efficacy in the SDSD group when there was a greater dosing interval between the first and second doses (Table 16 ,Table 17). The greatest efficacy seen was actually for > 12 weeks between doses, however this is based upon small numbers and there are a number of other factors that make the data difficult to analyse.

Table 17: Vaccine efficacy for incidence of first SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring > 15 days post second dose by dose interval (SDSD seronegative for efficacy analysis set)

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

VE of AZD1222 versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.
VE is defined as 1-(incidence of the infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 endpoints were based on adjudicated events.
Source: Supplemental Table IEMT53.3.1 – 4.

Table 18: Vaccine efficacy for incidence for first SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring more than 15 days post second dose by dose interval (SD seronegative efficacy analysis set)

Pooled (COV002 + COV003)					
≥ 4 weeks	27 / 4404 (0.61)	71 / 4405 (1.61)	62.26	41.24, 75.76	<0.001
≥ 4 – < 8 weeks	14 / 2146 (0.65)	25 / 2074 (1.21)	47.36	-1.18, 72.62	0.054
≥ 8 weeks	13 / 2258 (0.58)	46 / 2331 (1.97)	70.66	45.73, 84.14	<0.001
≥ 8 weeks – 12 weeks	12 / 1727 (0.69)	37 / 1777 (2.08)	66.48	35.76, 82.51	<0.001
4–12 weeks	23 / 3639 (0.63)	58 / 3625 (1.60)	60.86	36.61, 75.84	<0.001
Any interval	27 / 4440 (0.61)	71 / 4455 (1.59)	62.10	39.96, 76.08	<0.001

Subjects who had a longer dose interval had also longer follow up time after the first and second dose. Patients with a longer duration of follow up would have had increased time for exposure.

Patients with a longer dose interval were younger, thus it may be that the impact of dose interval is confounded by age. The mean age of those followed up 4-12 weeks was 43.6years, 10.7% were over 65 years. The mean age of those followed up more than 12 weeks was 39 years, with only 1% over 65 years.

And furthermore, that the number of patients exposed in the 6-8 week dosing interval was very small.

However, the increasing efficacy with increasing duration between the first and second doses is supported by the immunological analysis. SARS-CoV-2 spike protein antibody levels increased after the second dose with increasing duration between the first and second dose (Table 18,)

Table 19: Quantification of SARS-CoV-2 spike protein antibody levels for SD group by dose interval in the seronegative group

Visit Window	Statistic	SDSD AZD1222 < 6 wks N=677	SDSD AZD1222 6-8 wks N=239	SDSD AZD1222 9-11 wks N=169	SDSD AZD1222 ≥ 12 wks N=235
Baseline	N	481	137	110	154
	GMT	**60.51**	**58.02**	**48.79**	**52.98**
	95% CI for GMT	(54.1, 67.7)	(46.3, 72.6)	(39.6, 60.1)	(44.4, 63.2)
	Min, Max	16.5, 71694.0	16.5, 7228.0	16.5, 4497.0	16.5, 827.0
Day 28 post the first dose	N	479	99	87	152
	GMT	**8734.08**	**7295.54**	**7492.98**	**8618.17**
	95% CI for GMT	(7883.1, 9676.9)	(5857.4, 9086.7)	(5885.1, 9540.2)	(7195.4, 10322.3)
	Min, Max	16.5, 126108.0	426.0, 84533.0	46.0, 82133.0	93.0, 263135.0
Day 28 post the second dose	N	443	116	106	154
	GMT	**22222.73**	**24363.10**	**34754.10**	**63181.59**
	95% CI for GMT	(20360.5, 24255.3)	(20088.5, 29547.3)	(30287.2, 39879.8)	(55180.1, 72343.4)
	Min, Max	101.0, 178580.0	40.0, 276501.0	3590.0, 579194.0	4612.0, 767654.0

Age:

There were insufficient number of cases in participants aged > 56 years to make any meaningful analysis of the results for efficacy with age.

Table 20: Efficacy in the SDSD seronegative population stratified by age more than 15 days post second dose

	Cases/population AZD 1222	**Cases/population control**	**VE**
Subjects age 18-55 years	26/4099	70/4136	62.9 (41.86-76.35)
Subjects age over 56 years	2/718	3/700	
Subjects over 65 years	1/341	1/319	

Analysis of immunological data by Ramasay in section 19 demonstrated that patients over 55 years had similar immune response based on antibody levels and T cell response, however in

the clinical study there was a slightly lower increase in antibody and T-cell response with age. This was attributable to a shorter dose interval and shorter duration of follow up.

Low dose

Greater efficacy in the lower dose has been noted in the statistics for vaccine efficacy. However, there are a number of important confounding factors that limit the interpretation of this data.

These include:

1. Impact of dose interval

More patients in the LD group had a dose interval > 28 days.

Table 21: Time between vaccinations in the LDSD and SDSD group

Regimen	Duration of Interval between first and second doses				
	< 6 weeks	6-8 weeks	9-11 weeks	12+ weeks	Total
LDSD	0	12	766	1963	2741
SDSD	3400	1083	2166	2246	8895
Total	3400	1095	2932	4209	11636

There was a trend for better vaccine efficacy when there was a greater dose interval.

2. Younger age in the LDSD group

The mean age for seronegative LD was 39.5years, range 19-55. The mean age for the seronegative SD was 42.2 years, range 18 to 86 years.

The data on immunology in the elderly from the published papers and clinical study is limiting. However, immunosenesence is well described.

3. Impact on manufacturing site

All patients in LD group received vaccine from the Advent site. There is no data available for other efficacy analysis stratified by manufacturing site. The sponsor provided some immunological data by different site. This was difficult to interpret as the batches were rolled out to different centres at different stages in the pandemic so there are also other variable which would affect this.

4. All patients in that group were from the UK. At the time at the low dose was given, there was relatively low incidence of COVID-19 in the community.

It is also important to note that the immune response after the second dose from participants who received a LDSD regime was better than that seen in the SDSD regimen. Thus, it is also possible that the better efficacy in this group is a real phenomenon (Table 25).

Other subgroup analysis:

Seropositivity:
The analysis by subgroup was limited by the low number of seropositive participants. In addition, as these were recruited later they have had shorter period of follow up.

There was only 1 case of COVID in the seropositive control group and none in the vaccine group.

There were no seropositive cases with severe disease.

Country

The seronegative participants given a standard dose, there was very similar vaccine efficacy in the UK and Brazil. The number in South Africa were too small for meaningful analysis. The number of cases in the UK in the vaccine group was 15/2377, and in the control group 38/2430 giving an efficacy of 60.35% (95% CI 27.98-78.17%). For Brazil, the number of cases was 12/2063 in the vaccine group and 33/2025 in the control group, giving an efficacy of 64.17% (95% CI 30.65-81.5%, p=0.002).

Humoral Immunogenicity

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

RBD binding antibody response was closely correlated with S-binding response for all analyses. There was a strong induction of humoral immunogenicity for the combined SD and LD set as well as individual SD and LD set.

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 participants in the seronegative SDSD + LDSD group as well as individual SD and LD groups. A similar trend was observed for neutralising antibodies.

In seronegative patients at baseline, the mean GMT response after the first dose was similar to the mean GMT in seropositive patients at baseline. However, the range of GMT in seropositive patients at baseline was very large (around 400%). For seronegative patients at baseline, there was an increase in antibody titre at 28 days post first dose with a further increase at 28 days following the second dose. However in seropositive patients at baseline, there was a smaller increase in antibodies after the first dose with no further increase after the second dose.

Table 22: Quantification of SARS-CoV-2 S antibody levels over time by serostatus at baseline (SDSD for immunogenicity analysis set)

		Seronegative		Seropositive		Total	
Visit Window	Statistic	AZD1222 (N = 1320)	Control (N = 993)	AZD1222 (N = 36)	Control (N = 30)	AZD1222 (N = 1356)	Control (N = 1023)
Baseline	n	882	730	29	28	911	758
	GMT	57.18	55.43	13137.97	10966.21	67.98	67.38
	95% CI for GMT	(52.8, 62.0)	(50.9, 60.3)	(7441.8, 23194.1)	(5260.4, 22861.0)	(61.4, 75.2)	(60.3, 75.3)
	Min, Max	16.5, 71694.0	16.5, 7430.0	394.0, 465894.0	64.0, 177887.0	16.5, 465894.0	16.5, 177887.0
Day 28 post the first dose	n	817	665	28	28	845	693
	GMT	8386.46	57.24	175120.84	7303.99	9274.92	69.62
	95% CI for GMT	(7758.6, 9065.1)	(51.8, 63.3)	(120096.9, 255354.8)	(3307.9, 16127.4)	(8523.0, 10093.2)	(61.5, 78.8)
	Min, Max	16.5, 263135.0	16.5, 92439.0	8331.0, 728715.0	59.0, 102297.0	16.5, 728715.0	16.5, 102297.0
Day 28 post the second dose	n	819	667	28	25	847	692
	GMT	29034.74	61.88	112978.13	8296.39	30368.59	73.86
	95% CI for GMT	(27118.2, 31086.7)	(55.5, 69.0)	(72553.8, 175925.4)	(4233.6, 16258.1)	(28332.2, 32551.3)	(65.0, 83.9)
	Min, Max	40.0, 767654.0	16.5, 151193.0	1449.0, 753921.0	63.0, 91132.0	40.0, 767654.0	16.5, 151193.0

Table 23: Quantification of SARS-CoV-2 RBD antibody levels over time by serostatus at baseline (SDSD for immunogenicity analysis set)

		Seronegative		Seropositive		Total	
Visit Window	Statistic	AZD1222 (N = 1320)	Control (N = 993)	AZD1222 (N = 36)	Control (N = 30)	AZD1222 (N = 1356)	Control (N = 1023)
Baseline	n	882	730	29	28	911	758
	GMT	132.1	134.8	10175.8	8865.8	151.7	157.4
	95% CI for GMT	(126, 139)	(127, 143)	(5256, 19700)	(4306, 18253)	(141, 163)	(145, 171)
	Min, Max	102, 86502	102, 40456	102, 528893	102, 123988	102, 528893	102, 123988
Day 28 post the first dose	n	817	665	28	28	845	693
	GMT	7336.7	140.6	187069.6	6099.1	8167.8	163.7
	95% CI for GMT	(6718, 8012)	(131, 151)	(123651, 283015)	(2947, 12625)	(7431, 8978)	(149, 180)
	Min, Max	102, 302135	102, 97142	5224, 787498	102, 72343	102, 787498	102, 97142
Day 28 post the second dose	n	819	667	28	25	847	692
	GMT	37123.5	149.6	124043.1	6837.0	38633.9	171.8
	95% CI for GMT	(34519, 39925)	(138, 162)	(76484, 201176)	(3650, 12808)	(35901, 41575)	(156, 189)
	Min, Max	102, 952408	102, 104437	1028, 867490	102, 55734	102, 952408	102, 104437

Table 24: Quantification of Nab (live neutralization) antibody levels over time by serostatus at baseline (SDSD for immunogenicity analysis set)

		Seronegative		Seropositive		Total	
Visit Window	Statistic	AZD1222 (N = 1320)	Control (N = 993)	AZD1222 (N = 36)	Control (N = 30)	AZD1222 (N = 1356)	Control (N = 1023)
Baseline	n	114	24	3	0	117	24
	GMT	10.15	10.63	585.79		11.26	10.63
	95% CI for GMT	(9.1, 11.4)	(8.1, 13.9)	(6.6, >1858)		(9.5, 13.3)	(8.1, 13.9)
	Min, Max	7.5, 174.0	7.5, 51.0	73.0, 1858.0		7.5, 1858.0	7.5, 51.0
Day 28 post the first dose	n	113	36	2	0	115	36
	GMT	138.01	10.97	1858.00		144.39	10.97
	95% CI for GMT	(110.1, 173.0)	(8.6, 14.0)	(NE, NE)		(114.6, 181.9)	(8.6, 14.0)
	Min, Max	7.5, 1858.0	7.5, 96.0	1858.0, 1858.0		7.5, 1858.0	7.5, 96.0
Day 28 post the second dose	n	131	19	3	0	134	19
	GMT	423.11	10.76	1858.00		437.36	10.76
	95% CI for GMT	(363.1, 493.0)	(8.3, 14.0)	(NE, NE)		(374.9, 510.3)	(8.3, 14.0)
	Min, Max	41.0, 1858.0	7.5, 28.0	1858.0, 1858.0		41.0, 1858.0	7.5, 28.0

Patients receiving the LDSD regime had a lower antibody response to the first dose of vaccine, but higher antibody response after the second dose

Table 25: SARS CoV-2 antibody response in seronegative patients receiving AZ1222 by vaccine dose

	SDSD n=1320	**LDSD n=297**
Baseline	n=882 GMT 57.2	n=68 GMT 57.1
Day 28 post 1st dose	n=817 GMT 8386.46	n=68 GMT 5836
Day 28 post 2nd dose	n=819 GMT 29034	n=67 GMT 48 987

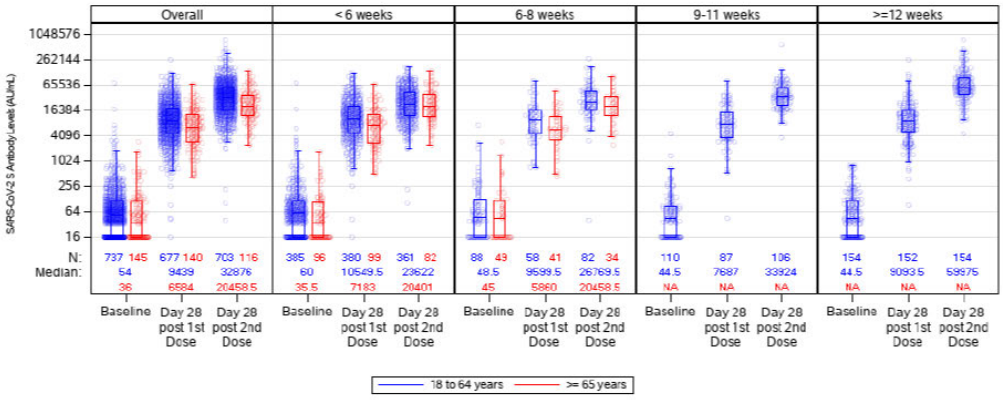
There was no difference in antibody responses in patients with or without co-morbidities. The GMT for S-binding and neutralising antibodies were lower in adults > 65 years of age in the clinical studies (Table 25, Table 26). However, when stratified by dosing interval immune response in the elderly was similar to in young people (Figure 5)

Table 26: SARS-CoV-s antibody in the combines SDSD seronegative group stratified by age in the AZD 1222 group

	Age 18-65 years	**Age > 66 years**
Baseline	n=737 GMT 59.58	n=145 GMT 46.4
28 days post 1st dose	n=677 GMT 8953.8	n=140 GMT 611.88
28 days post 2nd dose	n=703 GMT 30695.30	n=116 GMT 20727.02

Table 27: SARS Neutralizing antibody in SDSD seronegative group by age in the AZD 1222 group

	Age 18-65	**Age > 65 years**
Baseline	N=551 GMT 20	N=78 GMT 20
28 days post 1st dose	N=500 GMT 59	N=75 GMT 37
28 days post 2nd dose	N=497 G MT 173	N=52 GMT 109



Dose Schedule is the number of weeks between Dose 1 and Dose 2.
Boxplots display the median and 1st and 3rd quartiles. Whiskers extend to the minimum and maximum values, excluding outliers. Boxplots are created based on the log-normal distribution.
Titer values measured as below LLoQ (33) are imputed to a value that is half of the LLoQ. Titer values measured as above ULoQ (2000000) are imputed at the ULoQ. Participants with indeterminate and missing value of baseline serostatus are not included. Vaccine lot numbers are only displayed for active treatments.
S = Spike, LLoQ = Lower Limit of Quantification, ULoQ = Upper Limit of Quantification.
Source: Supplementary Figure IEMT132.1.1.

Figure 4: Quantification of SARS-CoV-2 S antibody stratified by age and dose interval in seronegative SDSD participants.

Cellular Immunity

IFNλ peaked by 14 days after vaccination and remained stable until at least 28 days post second vaccination. There was no further increase in IFN λ after the second dose.

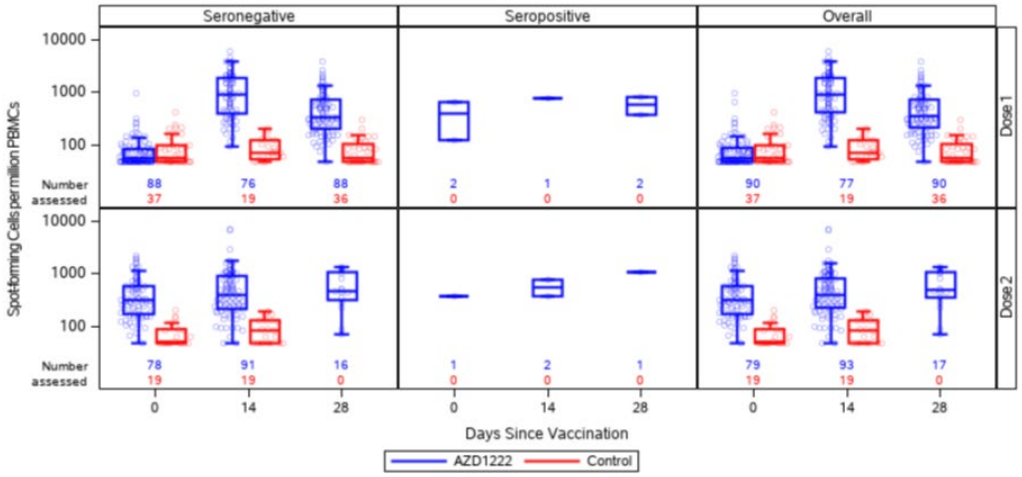


Figure 5: IFNλ+ spot forming cells over time post dose 1 and dose 2 by serostatus at baseline (SDSD for immunogenicity analysis set)

In the clinical studies, subjects aged over 65 years had a GMT for IFNλ similar to that seen in those aged 18-65 years.

Table 28: Quantification of IFNλ+ spot forming cells over time in SDSD seronegative group stratified by age

	Age 18-65 years	**Age over 65 years**
baseline	N=37 GMT 62.4	N=51 GMT 78.7
28 days post first dose	N=37 GMT 540.2	N=53 GMT 316.7
28 days post second dose	N=40 GMT 561.3	N=336.8 GMT 336.8

6.4. Evaluator's conclusions on clinical efficacy

The efficacy analysis consists of pooled interim data from 2 of the 4 ongoing clinical studies of the COVID vaccine. The interim analysis was pre-planned, the study was powered for statistical analysis on the primary endpoint.

There were a number of protocol changes during the clinical development program. These have introduced significant confounding and heterogeneity in to results. Although it is understandable, and recognised in the WHO and FDA guidelines that adaptive studies are required during a pandemic to take into account changes circumstances overtime, there is a need for regulatory decisions to be made on robust evidence, in particular when we are dealing with a vaccine to immunise the entire population.

The primary analysis population was seronegative group with SDSD or LDSD. Overall efficacy in this population was around 72%, the lower 95% confidence interval 54.8%. The efficacy reported in the LDSD group was higher. However, there are a number of confounding factors that make it unclear if the improved efficacy was due to the lower dose, or different age of the population, or different duration of follow up. Thus, the LD regime will not be considered for approval for regulatory purposes.

The efficacy in the SDSD population was around 62%, with lower 95% confidence interval 40%. Efficacy in both combined LSSD and SDSD seronegative populations and just SDSD seronegative population meets the criteria set by the EMA, FDA and WHO in relation to satisfactory efficacy of a COVID-19 vaccine. Although the best population for analysis could be debated, for regulatory purposes the outcome would be the same. In have reasonable confidence that the study design and conduct was sufficient for an estimate of the primary efficacy endpoint. One major limiting factor is the short duration of follow up. Thus any vaccine efficacy needs to be qualified by this issue. The short duration of follow up has the potential to bias the result toward not finding a treatment effect, as a longer duration of follow up increases the chance of exposure and the opportunity to prove efficacy.

Secondary analysis showed lower number of severe disease and hospitalisation in the AZD 1222 groups, however the numbers were small. There were less asymptomatic cases in the AZD 1222 than the control groups, which would suggest that the entire number of positive COVID-19 cases were lower in the AZD-1222 group. Further studies are required to determine if that vaccine has efficacy for asymptomatic disease and disease transmission

The vaccine efficacy after a single SD was around 60%-80%, efficacy begins 22 days after the first dose and extends at least 12 weeks after.

A post hoc analysis of the impact of duration between doses on efficacy was performed. Subgroup analysis demonstrated the vaccine efficacy after a second dose was similar regardless of dosing interval, perhaps greater at dosing intervals of > 12 weeks. The greater efficacy with wider dose intervals was supported by immunology assessments that demonstrated greater immune responses generated with wider dose intervals. There was no hypothesis proposed as to why this may be. I have concerns about over interpreting the impact of dose interval of efficacy without further confirmatory studies which minimise important confounders.

A major limitation of this study was the changes in protocol that occurred during the study and prevented a robust analysis of the impact of either a single or two doses, and the impact of dosing interval. This makes it very difficult to provide evidence based guidance on this. There will be further data on the efficacy and safety of a 28 day dosing interval from a current study in the USA, Peru, Chile.

The vaccine activated both a B cell and T cell response.

In addition to the limitations around dose and dosing interval, there are a number of significant limitations to the data.

> Firstly, the number of patients enrolled was 23 745. However, the primary efficacy data is from only 11 636 of these. The main reason for this seems to have been that many patients had only one dose, or developed COVID before the second dose, or were unable to be followed up. This problem will not be resolved with review of the final study report. However, further studies will provide more data in other populations.
>
> Secondly there is very limited data available for patients over 65 years. Immunological data is conflicting, with the study by Ramasay suggesting similar antibody and T-cell responses in the elderly and those age 18-59 years, but the clinical study demonstrating an antibody response in the elderly around 2/3 seen in younger people. The number of patients available for efficacy analysis was very small, particularly over 65 years. The ongoing study from the USA will overcome this limitation as it includes 25% of the study population over 635 years.
>
> Patients with significant co-morbidities and the immunosuppressed were excluded. It is known that patients with chronic respiratory disease, obesity, type 2 diabetes and hypertension are at increased risk of severe disease. These subjects will be included on ongoing safety studies.
>
> The follow up time was short, and there is a drop off in the number of participants as the time from the first or second vaccination increases. This makes the estimates of efficacy at longer intervals from dosing less accurate. The final analysis of data may overcome this limitation provided sufficient number of participants are able to be followed.

The duration of protection is unknown. Other ChAdOx1 vectors (such as MERS) have demonstrated immunity up to 12 months post vaccination. Long term efficacy will be demonstrated by following vaccinated subjects until the end of the study period for immunology and virology. It will also be assessed on ongoing studies in real world setting. As the vaccines start to be rolled out in a number of countries, efficacy studies are likely to be single arm and alternative statistical strategies will be required. Data on long term efficacy would be required for full registration.

7. Clinical safety

7.1. Studies providing evaluable safety data

Safety data was obtained from all participants of study COV001, COV002, COV003 and COV005. Safety was evaluated from solicited AE commonly associated with vaccines, unsolicited AE, SAE, and AESI. Biochemistry, haematology and other clinical laboratory tests were performed on a subgroup of participants.

Solicited AES were collected via diary cards in a subset of participants for 7 days following each vaccination. Most of the participants evaluated for solicited AEs were from UK and Brazil.

There were some differences in how solicited adverse events were collected in study CV005. Solicited AEs were assessed daily after vaccination from day 0 to 6 for COV005 and up to day 7 for other studies, by e-diary or diary card. In COV005, pain, warmth, malaise, nausea, vomiting, induration, feverishness and chills were not assessed. Bruising was only collected for COV005.

7.2. Patient exposure

As of 4th November 2020, 12020 participants received at least one dose of AZD 1222. Of these, 68% (8266) received 2 doses. 11724 participants were in the control group.

In the safety evaluation set, the median number of days of total exposure was 105 days in the AZD1222 group and 104 days in the control group. The median exposure after the second dose was 62 days in the AZD 1222 group, range 0-131 days, and 62 days in the control group, range 0-131 days.

In the safety data set, there were 19590 participants 18-55 years (82.5%), 2694 participants age 56-69 years (11.3%) and 1460 aged over 70 years (6.1%).

Older patients had a shorter duration of follow up.

Table 29: Duration of follow up in the AZD1222 group stratified by age (median and range)

	Age 18-64 years N=4099	**Age > 65 years N=341**
baseline	124 (41-149)	71 (41-85)
22 days post first dose	102 (19-127)	49 (19-63)
15 days post second dose	37 (1-79)	20 (1-38)

95% of participants were seronegative at baseline. There were 3% seropositive and 2% unknown.

7.3. Adverse events

7.3.1 SOLICITED

Local events:

Days 0-7 after the first vaccination, the number of local solicited adverse events was 75.7% in the vaccine group and 50.4% in the control group. Of the local adverse events in the vaccine group. 52.2% were mild, 13.0% were moderate, and 9.5% were severe (Table 29). The most frequent solicited AE were pain and tenderness. Pain was described in 54.2% and in most cases (44.7%) it was mild , severe pain was reported in 0.5%. The severity of local solicited AEs is described in Table 53.

Days 0-7 after the second vaccination, local solicited AE were less common occurring in 47.3% of the vaccine group and 30% of the control group.

Table 30: Local solicited adverse events 0-7 days after any dose of vaccine

	AZD 1222 N=12021 (%)	**Control N=11724 (%)**
ANY	2424 (75.7)	1574 (53.6)
Mild	1727 (53.9)	1207 (41.1)
Moderate	410 (12.8)	191 (6.5)
severe	287 (9.0)	176 (6.0)
Pain	1194 (52.6)	793 (39.4)
Tenderness	2101 (65.6)	1278 (43.6)
Redness	449 (14.1)	278 (9.5)
Warmth	390 (17.2)	311 (15.4)
Itch	304 (12)	229 (7.8)
Swelling	311 (9.8)	183 (6.3)
Induration	221 (9.7)	175 (8.7)
Bruising	165 (17.7)	60 (6.5)

Local AEs were of short duration, generally significantly improved by day 4 after immunisation (Table 31).

Table 31: Summary of local solicited AEs by showing duration

	Days 0 to 7 after any vaccination: AZD1222 N (%)							
Parameter	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Pain	434 (25.1)	776 (44.9)	505 (29.3)	290 (16.9)	133 (7.8)	63 (3.7)	28 (1.6)	18 (1.1)
Tenderness	908 (34.4)	1417 (53.7)	1205 (45.7)	867 (32.9)	564 (21.5)	283 (10.8)	133 (5.1)	45 (2.6)
Redness	14 (0.5)	25 (1.0))	54 (2.1)	48 (1.8))	39 (1.5))	27 (1.0)	15(0.6)	4 (0.2)
Warmth	141 (8.2)	184 (10.6)	97 (5.6)	58 (3.4)	42 (2.5)	22 (1.3)	11 (0.6)	8 (0.5)
Itch	156 (5.9)	139 (5.3)	131 (5.0)	107 (4.1)	91 (3.5)	69 (2.6)	48 (1.8)	8 (0.5)
Swelling	24 (0.9)	50 (1.9)	47 (1.8)	38 (1.5)	29 (1.1)	19 (0.7)	11 (0.4)	1 (0.1)
Induration	9 (0.5)	19 (1.1)	30 (1.7)	26 (1.5)	22 (1.3)	10 (0.6)	4 (0.2)	1 (0.1)
Bruising	80 (8.8)	97 (10.7)	76 (8.3)	47 (5.2)	43 (4.7)	35 (3.8)	23 (2.5)	0

Total participants evaluated was used as denominator in the percentage calculations
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.
Source: Table 1.5.1.4.2

Systemic events

Days 0-7 after vaccination, systemic adverse events occurred in 73% of those in the vaccine group and 59.6% of those in the control group. Of the vaccine group, 36.7% were mild, 27.9% were moderate, and 8.3% were severe. Fever occurred in 7.9% of the vaccine group and 1.2% of the control group. In the vaccine group, 33.6% described feverishness, 31.9% described chills, 26.4% joint pain, 44% muscle pain, 53% fatigue, 52.6% headache, 44.2% malaise, 21.9% nausea (Table 31) . One patient in the AZD 1222 group required hospitalisation for a fever.

Systemic events were less common after the second dose. Fever in 1.3% , feverishness 9.6%, chills 5.1%, joint pain 10.2%, muscle pain 19.3%, fatigue 27.8%, headache 26.9% , malaise 17.9%, nausea 8.4%.

Lymphadenopathy occurred in 32 patients in the vaccine group and 32 in the control group.

The severity of systemic solicited adverse events is described in Table 57

Table 32: Systemic solicited adverse events 0-7 days after any dose

	AZD 1222 N=12021	**Control N=11724**
ANY	2361 (73.7)	1809 (61.7)
Mild	1232 (38.5)	1229 (41.9)
Moderate	892 (27.8)	506 (17.2)
Severe	236 (7.4)	73 (2.5)
Emergency presentations	1	1

Fever	224 (7)	37 (1.3)
Feverishness	704 (31)	222 (11)
Chills	645 (28.4)	186 (9.2)
Joint pain	808 (25.2)	363 (12.4)
Muscle pain	1368 (42.7)	675 (23)
Fatigue	1739 (54.3)	1206 (41.1)
Headache	1663 (51.9)	1165 (39.7)
Malaise	939 (41.4)	424 (21.1)
Nausea	483 (21.3)	287 (14.3)
Vomiting	36 (1.6)	24 (1.2)

Local and systemic AEs were common the first day after injection, after day 5, the incidence decrease to < 2%.

Impact of Panadol:

In study COV001, prophylactic paracetamol use was given before and recommended regularly after vaccination (1 gram every 6 hours for 24 hours) in 2 of the 5 study sites. A total of 56 patients in the AZD 1222 group and 57 in the control group received prophylactic paracetamol. The incidence of pain, fever, chills, muscle pain, headache and malaise were lower in those that took paracetamol.

Table 33: The incidence of solicited adverse events in the 2 days after vaccination in participants with and without prophylactic paracetamol (COV001)

	Number (%) of Participants			
	AZD1222		MenACWY Control	
	No Paracetamol N=487	Paracetamol N=56	No Paracetamol N=477	Paracetamol N=57
Solicited Local Adverse Events				
Pain	320 (62.0)	24 (42.9)	148 (31.0)	12 (21.1)
Tenderness	382 (78.4)	42 (75.0)	243 (50.9)	20 (35.1)
Redness	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Warmth	83 (17.0)	8 (14.3)	53 (11.1)	6 (10.5)
Itch	7 (1.4)	1 (1.8)	7 (1.5)	1 (1.8)
Swelling	9 (1.8)	0 (0.0)	7 (1.5)	2 (3.5)
Induration	7 (1.4)	0 (0.0)	3 (0.6)	2 (3.5)
Solicited Systemic Adverse Events				
Fever	84 (17.2)	9 (16.1)	2 (0.4)	0 (0.0)
Feverishness	22 (50.1)	19 (33.9)	22 (4.6)	5 (8.8)
Chills	265 (54.4)	15 (26.8)	30 (6.3)	3 (5.3)
Joint Pain	142 (29.2)	14 (25.0)	24 (5.0)	2 (3.5)
Muscle Pain	283 (58.1)	24 (42.9)	74 (15.5)	10 (17.5)
Fatigue	310 (63.7)	33 (58.9)	157 (32.9)	15 (26.3)
Headache	312 (64.1)	27 (48.2)	116 (24.3)	11 (19.3)
Malaise	285 (58.5)	22 (44.6)	45 (9.4)	3 (5.3)
Nausea	111 (22.8)	14 (25.0)	27 (5.7)	5 (8.8)

The efficacy of paracetamol was not reproduced in studies COV002 and COV003. Participants in studies COV002 and COV003 were recommended to take paracetamol, and to self report in the diaries. However diary card data was provided for only 15.4% of participants and was missing data on paracetamol use for 52%. In this data set, local adverse events were seen in 86.4% of those who reported to take paracetamol and 77.6% who did not. Systemic adverse events were seen in 77.6% of those who reported to take paracetamol and 60.7% of those who did not.

7.3.2 UNSOLICITED

Unsolicited AEs were collected through until 28 days after each dose. The overall incidence of unsolicited AEs reported within 28 days of any dose was 37.8% in the AZD1222 group and 27.9% in the control group. The most common unsolicited adverse events were vaccination site pain, headache, pyrexia, myalgia, fatigue, chills, asthenia and malaise.

The overall incidence of unsolicited AEs reported ≤ 7 days of any dose was 32.2% in the AZD1222 group and 21.6% in the control group . Of these, 30% and 19% were considered related to the investigational product.

The overall incidence of unsolicited AEs reported > 7 days of any dose was 9.4% in the AZD1222 group and 9.0% in the control group

The majority of 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(1.9% AZD1222, 1.5% control)

Table 34: Unsolicited adverse events < 7 days post any dosing (≥2% in either treatment group, by preferred term (dose1 SD for safety analysis set)

Preferred Term (MedDRA version 23.1)	Number (%) of Participants[a] AZD1222 (N = 10069)	Control (N = 9902)
Vaccination site pain	1182 (11.7)	726 (7.3)
Headache	942 (9.4)	555 (5.6)
Pyrexia	828 (8.2)	179 (1.8)
Myalgia	813 (8.1)	307 (3.1)
Fatigue	455 (4.5)	248 (2.5)
Chills	377 (3.7)	87 (0.9)
Asthenia	251 (2.5)	106 (1.1)
Malaise	236 (2.3)	119 (1.2)

Table 35: Unsolicited adverse events by system organ class (any dose for safety analysis set)

System Organ Class	Number (%) of Participants[a] 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)

The most common adverse events by organ system class were general site and administrative conditions, neurological disorders, and musculoskeletal and connective tissue disorders.

The imbalance in nervous system disorders was mainly driven by headache, which occurred in 9.3% of subjects who received AZD1222 and 6.1% of the control group. The imbalance in headache was in the first 7 days after vaccination and considered by the sponsor to be due reactogenicity. The SAE related to transverse myelitis and myelitis are described below. There were six cases of facial paralysis, three in the AZD1222 group and 3 in the control group.

Tremor was also more commonly seen with AZD1222, it tended to be in the first 7 days, mild, and associated with other symptoms of reactogenicity.

The imbalance in musculoskeletal and connective tissue disorders was driven by arthralgia (1.4% vs 0.8%) and myalgia (7.6% vs 3.1%) and attributed to reactogenicity.

The imbalance in general and administrative disorders was driven by 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%).

The incidence and pattern of unsolicited AEs were similar in seropositive and seronegative participants.

Table 36: Adverse drug reactions described in the PI (pooled data set)

MedDRA SOC	Adverse reaction[b]	COVID-19 Vaccine AstraZeneca (N= 10, 069)	Control[c] (N= 9, 902)
Nervous system disorders	Headache	Very common (52.6%)	Very common (39.0%)
Gastrointestinal disorders	Nausea	Very common (21.9%)	Very common (13.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (44.0%)	Very common (21.6%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (12.4%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.7%)	Very common (39.5%)
	Injection site pain	Very common (54.2%)	Very common (36.7%)
	Injection site warmth	Very common (17.7%)	Very common (14.5%)
	Injection site redness (Injection site erythema)	Very common (14.0%)	Common (8.8%)
	Injection site itch (Injection site pruritus)	Very common (12.7%)	Common (7.5%)
	Injection site swelling	Very common (10.0%)	Common (5.8%)
	Systemic		
	Fatigue	Very common (53.1%)	Very common (38.2%)
	Malaise	Very common (44.2%)	Very common (20.2%)
	Feverishness[d] (Pyrexia)	Very common (33.6%)	Very common (10.7%)
	Chills	Very common (31.9%)	Common (8.3%)
	Fever[d] (Pyrexia)	Common (7.9%)	Common (1.2%)

[a] Frequencies of ADRs are reported from the safety analysis set where participants received the recommended dose (5×10^{10} vp) as their first dose.

[b] Solicited event reporting terms, where applicable MedDRA preferred terms are given in parentheses

[c] Control was either meningococcal vaccine or saline solution

[d] Defined as: Feverishness, (subjective) a self-reported feeling of having a fever; Fever, (objective) ≥38°C

7.3.1. Deaths and other serious adverse events

7.3.1.1. Integrated safety analyses

Fewer than 1% of participants reported an SAE (0.7% AZD1222, 0.8% control);
2 participants in the AZD 1222 group [pyrexia, and transverse myelitis] and 2 in the control group [autoimmune haemolytic anaemia and myelitis] experienced an SAE that the investigator considered may have been due to the study medication.
The case of pyrexia (40.5 degrees) was a 30yo black male in South Africa. The event occurred 2 days after vaccination and resolved with paracetamol.

There were 3 cases of angina in the AZD 1222 group and none in the control group, all reported between 16 and 17 days post vaccination and considered unlikely to be related to AZD 1222.

There were 5 deaths before 04 November 202 and one death after 04 November 2020. Two deaths occurred in the AZD1222 group (fungal pneumonia in a patient with HIV and malignant neoplasm) and 4 deaths occurred in the control group (COVID-19 pneumonia, craniocerebral injury, injury, and homicide). None of these events were considered treatment related by the investigator.

Details of SAE in the AZD1222 group

Transverse myelitis: 37 yo female. Family history of charcot marie tooth type 1a. Participant received 2 doses of AZD1222 on 2nd June and 20th August. The patient was taking certrazine for hay fever. 2 weeks after the second dose (3rd September), the patient experienced pain and weakness of both arms, altered sensation with bladder filling, reduced perineal sensation, reduced sensation in the torso, ataxic gait, poor hand strength and head ache. A provisional diagnosis of transverse myelitis was made. This started to improve the next day and continued to do so over the subsequent weeks. MRI of the cervical cord 3 days later on the 6th Feb showed high T2 signal intensity in the anterior aspect of the cervical cord extending 2cm longitudinally at C6-C7 consistent with an inflammatory lesion. On the 7th Feb, MRI of the brain showed multiple small non enhancing supratentorial lesions which were scattered periventricularly and in the cerebellum. There were also some enhancing periventricular lesions. Eye examination was normal. On the 9th September methylprednisolone was commenced despite the spontaneous improvement. On the 21st October, there was continuing improvement clinically and radiologically. There was some uncertainty among treating clinicians if this was inflammatory (and drug related) or vascular or MS.

Multiple sclerosis: 37 yo female. Day 10 after first dose developed paraesthesia. Spine and brain MRI demonstrated multiple lesions, most were thought to pre-date the vaccination). The MS was considered not related to study medication.

Details of SAE in the control group

Myelitis: 48 year old male. On the 12th June, received the MenACWY vaccine. On the 5th August, 54 days after the dose, experienced a subacute onset of lower limb paraesthesia which persisted for 1 week. MRI on that day revealed an ovoid, T2 high signal lesion at the centre of T5 that enhanced with contrast. On the 14th August, clinical examination revealed reduced sensation to pinprick over the lateral borders of the feet, medial aspect of the knees and anterior aspect of the thighs. He did not receive any treatment and recovered spontaneously.

7.3.2. Discontinuations due to adverse events

Very few patients discontinued due to AEs.

7.4. Evaluation of issues with possible regulatory impact

7.4.1. Liver function and liver toxicity

7.4.1.1. Integrated safety analyses

There were no cases of severe liver injury. There was no pattern of concerning changes in liver function tests.

7.4.2. Renal function and renal toxicity

7.4.2.1. Integrated safety analyses

There was no reports of significant renal impairment. There were no significant concerns about changes in serum chemistry.

7.4.3. Other clinical chemistry

7.4.3.1. Integrated safety analyses

No concerns

7.4.4. Haematology and haematological toxicity

7.4.4.1. Integrated safety analyses

No concerns

7.4.5. Adverse Events of Special Interest

The adverse events of special interest included the following:

AESI	**concept**
Neurologic	Generalized convulsion: Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: GBS is a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: ADEM is defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: These events would include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Haematological	Thrombocytopenia: Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per μL.
Vascular	Thrombotic, thromboembolic, and neurovascular events: These are events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate
Immunological	Vasculitides: Vasculitides are a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: Anaphylaxis an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention

	Vaccine-associated enhanced respiratory disease: The pathogenicity of VAERD has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia VAERD may manifest as a severe form of respiratory disease with prolonged fever, and diverse clinical manifestations of disease severity and pathological changes marked by increased areas of lung consolidation, broncho-interstitial pneumonia, and necrotizing bronchiolitis
	Potential immune-mediated conditions: These conditions are a group of autoimmune inflammatory disorders characterized by an alteration in cellular homeostasis, which may or may not have an autoimmune aetiology.

7.4.5.1. Integrated safety analyses

The overall incidence of AESIs was very low, 5 (0.8%) in the AZD1222 group and 126 (1.1%) in the control group

There were no clinically meaningful imbalances in the incidence of AESIs by category or PT between the AZD1222 and control group except for VAERD.

Ten (0.1%) participants reported COVID-19 and 2 (< 0.1%) suspected COVID-19 in the AZD1222 group; 21 (0.2%) participants reported COVID-19 and 2 (< 0.1%) COVID-19 pneumonia in the control group. These were described as VAERD in the safety analysis, however it was unclear how VAER was defined. Only 2 cases were severe, both in the control group.

The most frequently reported (≥ 5 participants in the AZD1222 group) neurologic AESIs by PT were paraesthesia (37 [0.3%] vs 48 [0.4%] control), hypoaesthesia (13 [0.1%] vs 19 [0.2%] control), and muscular weakness (7 [0.1%] vs 9 [0.1%] control).

7.4.6. Immunogenicity and immunological events

7.4.6.1. Integrated safety analyses

There was a case of anaphylaxis in the AZD 1222 group 63 days after vaccination. The patient was taking antibiotics for tonsillitis at the time.

There was a case of angioedema 8 days after vaccination in the AZD1222 group and at a time the participant ingested crab.

7.4.7. Pregnancy

7.4.7.1. Integrated safety analyses

Pregnancy was reported for 21 subjects, 12 in the AZD1222 group and 9 in the control group. Of these pregnancies, 5 resulted in spontaneous abortion – 2 in the AZD1222 group and 3 in the control group. The outcome of these pregnancies is unknown.

7.4.8. Viral shedding

No submitted data from humans. In previous animal studies using the ChAdOx1 vector, there was no shedding of the chimpanzee adenovirus vector.

Infection and shedding of COVID 19 is possible after vaccination, even if the patient is asymptomatic. This was demonstrated in clinical studies by the number of symptomatic and asymptomatic cases in the vaccine group. In a SARS-CoV-2 study in rhesus monkeys, vaccination with AZD 1222 reduced viral load and viral replication in the lower respiratory tract, but had not effects on viral load or shedding in the upper respiratory tract.

7.5. Other safety issues

7.5.1. Safety in special populations

By age

Overall, 2109 (8.9%) of participants were over 65 years and 1460 (6.1%) of all study participants over 70 years. In relation to reactogenicity, solicited local and systemic adverse events were milder and reported less frequently in older adults (> 65 years) compared to younger adults.

Table 37: Overall summary of unsolicited adverse events within 7 days of dosing in subjects age 18-65 years

	Number (%) of Participants	
Participants[a] with at least one	AZD1222 (N=10852)	Control (N=10784)
Within 7 days after vaccination		
Unsolicited AE	3661 (33.7)	2400 (22.3)
Investigational product-related unsolicited AE	3312 (30.5)	1993 (18.5)
Unsolicited AE by maximum severity[b]		
≥ Grade 3 severity[b]	138 (1.3)	89 (0.8)
Any AE with outcome of death	0	1 (<0.1)
Serious[c] AE	14 (0.1)	10 (0.1)
Serious[c] and/or ≥ Grade 3 severity[b] AE	140 (1.3)	92 (0.9)
Investigational product-related serious[c] AE	1 (<0.1)	0
AESI	39 (0.4)	51 (0.5)
Investigational product-related AESI	23 (0.2)	31 (0.3)

AE = adverse event; SAE = serious adverse event; AESI = adverse event of special interest; Related = possible, probably or definitely related according to the investigator.
[a] 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.
[b] Grade 3: Severe, Grade 4: Life-threatening. Grade 5: death. Grade 5 is only collected for COV005.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the Participant).
Unsolicited AEs, SAEs and AESIs summarized from the start of each dose until Day 7.

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Table 38: Overall summary of unsolicited adverse events within 7 days of dosing in subjects over 65 years

	Number (%) of Participants	
Participants[a] with at least one	AZD1222 (N=1169)	Control (N=940)
Within 7 days after vaccination		
Unsolicited AE	208 (17.8)	127 (13.5)
Investigational product-related unsolicited AE	163 (13.9)	101 (10.7)
Unsolicited AE by maximum severity[b]		
≥ Grade 3 severity[b]	5 (0.4)	5 (0.5)
Any AE with outcome of death	0	0
Serious[c] AE	2 (0.2)	2 (0.2)
Serious[c] and/or ≥ Grade 3 severity[b] AE	5 (0.4)	5 (0.5)
Investigational product-related serious[c]AE	0	0
AESI	3 (0.3)	3 (0.3)
Investigational product-related AESI	2 (0.2)	1 (0.1)

AE = adverse event; SAE = serious adverse event; AESI = adverse event of special interest; Related = possible, probably or definitely related according to the investigator.
[a] 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.

By co-morbidity

In the safety analysis set, 4626 (19.5%) of participants were obese, 1481 (6.2%) had hypertension, 2482 (10.5%) had respiratory disease, 629 (2.6%) had diabetes and 2975

(12.5%) had pre-existing cardiovascular disease including 3 patients with heart failure and 63 with ischaemic heart disease. There was no imbalance of reactogenicity or unsolicited AEs by co-morbidity. However patients with significant co-morbidities were excluded from the studies.

By seropositivity

Overall, the number of solicited AEs reported after any vaccination was lower in the seropositive group, the number of ≥ 3 systemic solicited AEs was similar, however the number of ≥ grade 3 local solicited AE was higher in the seropositive group.

Table 39: Summary of solicited AEs in seropositive patients day 0-7 days after vaccination in SD1 safety set

	Number (%) of Participants	
Participants[a]	AZD1222 (N = 321)	Control (N = 350)
Evaluated for solicited AEs	160	179
Any solicited AE	130 (81.3)	102 (57.0)
Any local solicited AE	110 (68.8)	62 (34.6)
Any >= Grade 3 severity local solicited AE	24 (15.0)	10 (5.6)
Any systemic solicited AE	109 (68.1)	83 (46.4)
Any >= Grade 3 severity systemic solicited AE	13 (8.1)	6 (3.4)

Abbreviations: AE = Adverse Event.
[a]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 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, 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.

7.5.2. Safety related to drug-drug interactions and other interactions

No data. Receipt of any vaccine within 30 days before or after the study intervention was not allowed, except for seasonal influenza and pneumococcal vaccine which were permitted at least 7 days before or after the vaccine.

7.6. Post marketing experience

The following severe cases in the SOC Nervous System Disorders have been described in study an ongoing Phase III study in USA/Brazil and Chile (D8110C0001) . This study remains blinded.

ID	First dose	Last dose	Date of event	SAE preferred term	Relationship to investigational product
20052830130 52yo Asian male	2/11/20	2/11/20	17/11/20	Cerebrovascular event	Not related
20053630131 70yo white male	24/11/20	22/12/20	3/12/20	Cerebrovascular event	Not related
20052960024 64yo white female	4/9/20	4/9/20	18/9/20	Chronic inflammatory demyelinating polyradiculopathy	related

20053500153 55yo white male	3/12/20	3/12/20	10/12/20	Dizziness	Not related
20053180031 40yo white female	12/11/20	12/11/20	5/12/20	IVH	Not related
20052960211 68yo white male	6/11/20	3/12/20	16/11/20	Ischemic stroke	Not related
20053140147 71 yo white male	2/12/20	4/1/20	21/12/20	Myocardial infarction	Not related
20053220048 39yo white female	4/11/20	4/11/20	19/11/20	Peripheral sensory neuropathy	Not related
20052640352 83yo white male	24/11/20	22/12/20	4/1/21	Syncope	Not related

The sponsor was requested to provide any available data from post market distribution. As of 17th January, 2 321 300 doses of AZD122 had been distributed to the UK. A Licence partner of AZ was distributing 11 million doses to the Indian government.

There is no information about the number of doses that have been administered. The monthly safety reports which are part of the EU-RMP (and Australian RMP) will include an estimate of vaccine exposure as well as safety data. There will be tables stratified by age.

7.7. Evaluator's overall conclusions on clinical safety

Data on safety is from 1202 exposed participants in ongoing clinical studies. All patients had one dose, 68% had 2 doses. The median duration of follow up was 105 days after the first dose and 61 days after the second dose.

Overall, the COVID-19 vaccine caused more local and systemic AEs than meningococcal vaccine. However most AEs were mild or moderate and lasted only a few days.

There is limited data available for the impact of paracetamol. Data from a small group of patients in COV001 showed some reduction in symptoms, this was not replicated in the studies COV002 and COV003 although data collected from those studies was poor.

There were no deaths attributed to the vaccine. There was a case of transverse myelitis and multiple sclerosis in the vaccine group, and one case myelitis in the control group, all unlikely to be related to the vaccine. There was an unusual case of chronic inflammatory demyelinating polyneuropathy in the ongoing US study, it is uncertain if this related to AZD1222. There is a precaution in the PI that states : *"very rare events of demyelinating disorders have been reported*

following vaccination with COVID-19 Vaccine Astra Zeneca. A causal relationship has not been established." Immune mediated adverse events are included as potential risks in the RMP. I am satisfied that the current pharmacovigilance and risk mitigation data deal with this potential risk.

There is insufficient data to be sure if the cases of pneumonia described as VAERD met all of the criteria for this. As < 5% of participants were seropositive, the safety dataset is not sufficient to eliminate this potential risk. In addition, it is recognised that VAERD may not become apparent until after efficacy wanes. There was no risk of VAERD in the animal studies. The potential risk of VAERD in included in the RMP.

There is very little safety data in the elderly, there were only 2109 (8.9%) of participants over 65 years and 1460 (6.1%) of all study participants over 70 years. Reactogenicity was less severe in the elderly than in the younger population. This is a relatively small sample of at risk individuals that have been assessed for safety. The elderly at a high risk of COVID-19, and according to the WHO guidance documents pre-market studies should include sufficient number of subjects at risk of severe disease.

Although around one third of the safety population were noted to have a co-morbidity, most of these co-morbidities were mild. Obesity, type 2 diabetes, hypertension and respiratory disease are known risk factors for severe COVID-19. I do not consider there to be sufficient information about the safety in these populations with more severe co-morbidities.

There is no data in immunosuppressed patient population.

There is minimal data for use in pregnancy.

Ongoing Studies

Studies in the meta-analysis:

The COV001, COV002, COV003 and COV005 studies are fully enrolled. Paediatric studies have not yet been initiated.

It is estimated that the final data analysis of the studies included in this dossier, after 12 months of follow up, will be available in the first half of 2022.

Long term follow up will be for 12 months. Long term immunity will be assessed by planned analysis of immunology and virology during the study. It is likely that participants in the control groups will be vaccinated as part of the roll out vaccination programmes in their countries. The sponsor acknowledges that this may require a change in statistical analysis to deal with the drop outs.

Post approval safety studies will further expand evidence on the occurrence of COVID-19 and severe COVID-19 disease over time among people vaccinated with AZD 1222. Study COVIDRIVE D8111R00005 will primarily evaluate an association between hospitalisation for COVID-19 and vaccination with AZD1222. Long term data collection from real world use will inform the durability of protection over time.

US study:

D8110COV00001 is a large study being conducted in USA, Peru and Chile which includes 25% of participants over 65 years. It is estimated that the interim analysis of this study will be available in March 2021. The dosing interval in this study is 29 days (range 26-36).

Table 40: AZD 1222 efficacy study status and data availability

Study	Locations	Current status	N of vaccinated participants as of DEC 2020	Next data-cut off (current status)	Next database lock (current status)	Availability of data for subm-ission (current estimate)	Comments
Pooled analysis of COV001/2/3/5	See below	Ongoing	23745	07 DEC 2020	11 JAN 2021	End MAR 2021	
COV001	UK	Ongoing	1067	Final: NOV 2021	Final: DEC 2021	MAR 2022	
COV002	UK	Ongoing	10663	Final: DEC 2021	Final: JAN 2021	APR 2022	
COV003	Brazil	Ongoing	10002	Final: JAN 2022	Final: FEB 2022	MAY 2022	
COV005	South Africa	Ongoing	2013	Final: DEC 2021	Final: JAN 2022	APR 2022	
D8110C00001	USA, Chile, Peru	Ongoing	25711	31 DEC 2020	IA: mid-late JAN 2021	End MAR 2021	Event-driven; dates are estimates
D8111C00001	Russia	On hold	0	To be determined	To be determined	To be determined	On hold by Ministry of Health until further notice
D8111C00002	Japan	Ongoing	256 (1 dose) 237 (2 doses)	21 DEC 2020	IA: 01 FEB 2021	IA: 19 MAR 2021 PA: 26 APR 2021	IA: n=99 Immuno, 256 Safety PA: n=256 Immuno, 256 Safety
COV004	Kenya	Ongoing	20	TBD: 2022	TBD: 2022[a]	TBD: 2022	
COVISHIELD	India	Ongoing	1600	14 DEC 2020	IA: 14 DEC 2020	Interim report provided on 24 DEC 2020	Report anticipated mid-end FEB 2021 with all cleaned safety and immuno data available up to Day 57 (1 month after dose 2)

IA Interim analysis. PA Primary analysis. Immuno Immunogenicity

[a] No IA planned

No further studies of the LDSD regimen will be performed.

It is unclear at this time if there will be further studies of dosing interval.

Table 41: Ongoing pharmacovigilance studies

	objectives	**milestones**
Enhanced active surveillance study A phase IV enhanced active surveillance study of people vaccinated with AZD 1222	Primary objective: To assess the safety and tolerability of at least 1 dose of AZD 1222 in adults ≥18 years after vaccination with the first dose Secondary objective: To assess the long term safety and tolerability of AZD 1222 in adult over 18 years who have received 1 dose Pregnancy substudy	Study protocol available March 2021
Pregnancy registry		
Post market safety study – post marketing observational study using existing secondary health data sources to evaluate the association between	Investigate safety concerns and AESI in recipient and non-recipients of AZD 1222 among all populations studies	Protocol available April 2021

exposure to AZD 1222 and safety concerns	including populations with missing information.	
Post-marketing effectiveness study: Post authorisation/ post marketing retrospective cohort study to evaluate the effectiveness of the AZD 1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public partnership with COVIDRIVE utilising primary data collected prospectively through the COVIDRIVE platform	To estimate brand specific vaccine effectiveness against laboratory confirmed SARS-CoV-2 in hospitalised patients overall and by age group (< 18 years, 18-64 years, > 65 years) after adjusting for possible confounders	Study protocol expected March 2021

8. Clinical questions asked during the submission

A number of questions were asked during the evaluation. The responses have been noted and incorporated in the report when relevant.

8.1. Additional expert input

Statistical report: TRIM D21-2067875

Advice in relation to case of transverse myelitis: TRIM D21-2104574

9. Risk Benefit Assessment

The world is in the midst of a pandemic associated with COVID-19. As of the 12th January 2021 there have been 88 387 352 people infected and 1 919 204 people die from the disease. In addition, the virus and associated measures to control it has had an impact on the economy and quality of life for a significant proportion of the population. Although in Australia we have had relatively few cases and deaths compared to other nations, controlling the outbreaks has led to a significant disruption to our lives. The public have been waiting for a vaccine as they have been told for months that a vaccine is the solution to this loss of freedom.

Astra Zeneca has applied for provisional registration of AZD 1222 on the basis of an interim analysis of a meta-analysis of clinical studies. This early data suggests an efficacy of around 62% for the use of SDSD regime against symptomatic COVID disease with a median duration of 48 days after the second dose. Analysis of secondary and exploratory endpoints suggests that the vaccine is effective against severe disease. Efficacy against asymptomatic spread is unknown.

There are a number of limitations in the study design and conduct which introduce potential confounding factors and bias. In particular the efficacy analysis was performed on only around 50% of the population initially enrolled. A loss of power of the study like this would reduce the chance of the sponsor demonstrating efficacy. Yet despite this, efficacy was demonstrated. And results were consistent among most subgroups. The EMA and FDA guidelines for COVID-19 suggest that a vaccine efficacy of over 50% and a 95% confidence interval of over 30% would be supportive of registration during this pandemic.

There is very limited data in elderly, those with significant co-morbidities and the immunosuppressed. These groups are known to respond less well to all vaccines. Yet they are a high risk group of infection and severe infection. Ideally, data in these group would be available prior to registration. However, in the context of current pandemic there is some urgency to protect the most vulnerable of our population. I am of the opinion that use of the vaccine in these groups should be allowed providing health care professionals adequately asses and inform patients of the risks and benefits to their individual situation. Further data on these subgroups will become available over the next few years as a result of ongoing efficacy and safety study. I recommend the delegate consider the need to make the collection of this data a condition of registration.

Follow-up is limited. The Kaplan Meier curves demonstrated increasing efficacy over time. However, this may be confounded by the decrease in patient numbers followed up by longer periods. The duration of immunity induced by this vaccine is unknown. Long term safety is unknown, however most AEs related to a vaccine would occur soon after vaccination.

Evidence on the optimal dose (single of two doses) and dosing interval is preliminary. The data available suggest similar efficacy from a single dose or booster dose of SD vaccine. Efficacy of a single dose was demonstrated for at least 12 week. The timing of the second dose varied in the studies from < 6 weeks to 24 weeks. There are currently no ongoing studies investigating the optimal dosing interval. The study in USA, Peru, Chile is evaluating a 4 week dosing interval. It is recommended the sponsor consider further studies into the benefits of two over one dose and the optimal dosing interval. From a regulatory perspective, the dosing interval proposed for 4-12 weeks is appropriate and enables health care providers and the Australian Immunisation taskforce to be more flexible in their recommendations.

10. Recommendation regarding authorisation

For provisional registration, the role of the TGA is to assess whether the 'quality, safety and efficacy' have been adequately established for the purpose for which the goods are to be used. For a vaccination to be rolled out with the aim of protecting the Australian population, the context of this use needs to be considered.

As the clinical evaluator, I can comment only on the clinical data submitted. The primary efficacy endpoints for the prevention of symptomatic COVID-19 meets the EMA and FDA requirements for COVID vaccines. There needs to be consideration as to whether the efficacy demonstrated is sufficient for use in the Australian context where COVID-19 is less prevalent. This will require expert advice. Apart from local and systemic signs of reactogenicity typical of vaccines, there were no significant safety concerns.

Although it is understandable that the clinical development plan needed to evolve in the context of the pandemic and as more knowledge about the vaccine and COVID-19 became available. There are significant concerns about the robustness of the data: the study design was not entirely fit for purpose to evaluate efficacy in high risk groups, there is insufficient data about dosing, there were a number of patients lost to efficacy analysis.

I have the following recommendations to the wording of the indication and PI if the vaccine is to be approve:

1. I recommend a change in the wording of the indications to reflect other vaccines registered for COVID-19.
2. The limitations of the data in the elderly, immunosuppressed and pregnant women will be made clear in the precautions sections. It is recommended that these patient speak to their GP or a specialist physician about the risks and benefits of the vaccine for them.

3. The dosing interval proposed for 4-12 weeks is acceptable.

4. The clinical trial section should be limited to the primary efficacy analysis

11. Comments in relation to the product documentation

11.1. Comments about the PI

See attached document

11.2. Comments about the summary of safety concerns

The summary of safety concerns, as described in the EU RMP is as follows

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	• Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED)
Missing Information	• 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

Other important potential risks include

- use of a GMO

Other missing information

- use in elderly
- use with significant co-morbidities.

12. References

Voysey, M etal. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa and the UK. Lancet. Published online Dec 8 2020

Safety and Immunogenicity of ChAdOx1CoV-19 vaccine administered in a prime boost regimen in young and old adults (COV002): a single blind, randomised, controlled phase 2/3 trial. Lancet Published online Nov 19. 2020

Folegatti, PM; etal. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2 , single blind, randomised controlled trial. Lancet 2020 Aug 15; 396; 467-478

Ewer KJ, Barrett JR et al. T cell and antibody responses induced by a single dose of ChAdOx1nCoV-19 (AZD1222) vaccine in a phase ½ clinical trial. Nature Medicine (https://doi.org/10.1038/s41591-020-01194-5)

FDA: Development and Licensure of vaccines to prevent COVID-19. Guidance for Industry. June 2020

WHO: Design of vaccine efficacy trials to be used during public health emergencies- points of consideration and key principles.

EMA. EMA considerations on COVID-19 vaccine approval. 16th November 2020.

13. Supporting information, tables and figures

13.1. Published literature in relation to immunogenicity

13.1.1. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime boost regimen in young and old adults (COV002): a single blind, randomised, controlled, phase 2/3 trial

Ramasamy MN; Minassain AM et al. Lancet Nov 19, 2020

This report describes the effect of two different doses, 2.2 X 10^{10} virus particles and 3.5-6.5 X 10^{10} virus particles in adults of different age cohorts.

Two different batches of the vaccine were used from two different manufacturing sites. One manufactured and vialed by Advent (Pomezia, Italy) and one manufactured by COBRA biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK). The 18-55 year cohort received the vaccine by COBRA, other groups received the vaccine by Advent.

All participants had clinical and immunological assessments at 0, 7, 14, and 28 days after the prime and booster vaccine. Participants in the 18-55 year low dose group had assessments at baseline, immediately before the boost dose and 14 and 28 days after their boost dose.

Humoral responses at baseline and after vaccination were assessed using Meso Scale Discovery multiplexed immunoassay against spike and receptor binding domain [RBD], a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, and a live SARS-CoV-2 microneutralisation assay MNA80, which was done at Public Health England (Porton Down, UK), as described previously. Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells. Neutralising antibodies to the ChAdOx1 vector were measured using a secreted embryonic alkaline phosphatase (SEAP)-reporter assay, which measures the reciprocal of the serum dilution required to reduce in-vitro expression of vector-expressed SEAP by 50%, 24 h after transduction.

Comparisons across different age groups were performed using Kruskal Wallis tests within each dose level of the vaccine, or unadjusted analysis of variance applied to log-transformed values for neutralisation titres. Comparisons between the low dose and standard dose groups were done using Wilcoxon rank sum tests or independent sample t-tests.

Results:

Five hundred and sixty participants were enrolled in the study and randomly assigned to the experimental vaccine or control group. There were 160 participants in the 18-55 year age group (100 to the ChAdOx1 nCoV-19), 160 aged 56-69 (120 assigned to ChAdOx1 nCoV-19) and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19).

Using a multiplex immunoassay that detected total IgG against RBD and trimeric spike protein, similar antibody titres were observed for those who received a standard or low dose (Figure 4). The antibody levels after a single dose peaked at 28 days, and remained stable for those who did not have a booster dose. There was an increase in antibody titre seen in those who had a booster dose. Antibody titres after the first dose were slightly higher in the 18-55 year age group than the older age group, however after the second dose this difference was no longer seen. Similar results were seen with RBD antibodies and with an in house standardised ELISA.

In a live SARS-CoV-2 microneutralisation assay (MNA_{80}) median titres peaked by day 42 in most groups that received 2 vaccinations. There were no differences between the low and standard dose groups and between age groups. Neutralisation titres were seen by 14 days after the boost vaccination in 99% of participants. Anti-spike IgG levels were highly correlated to neutralising titres.

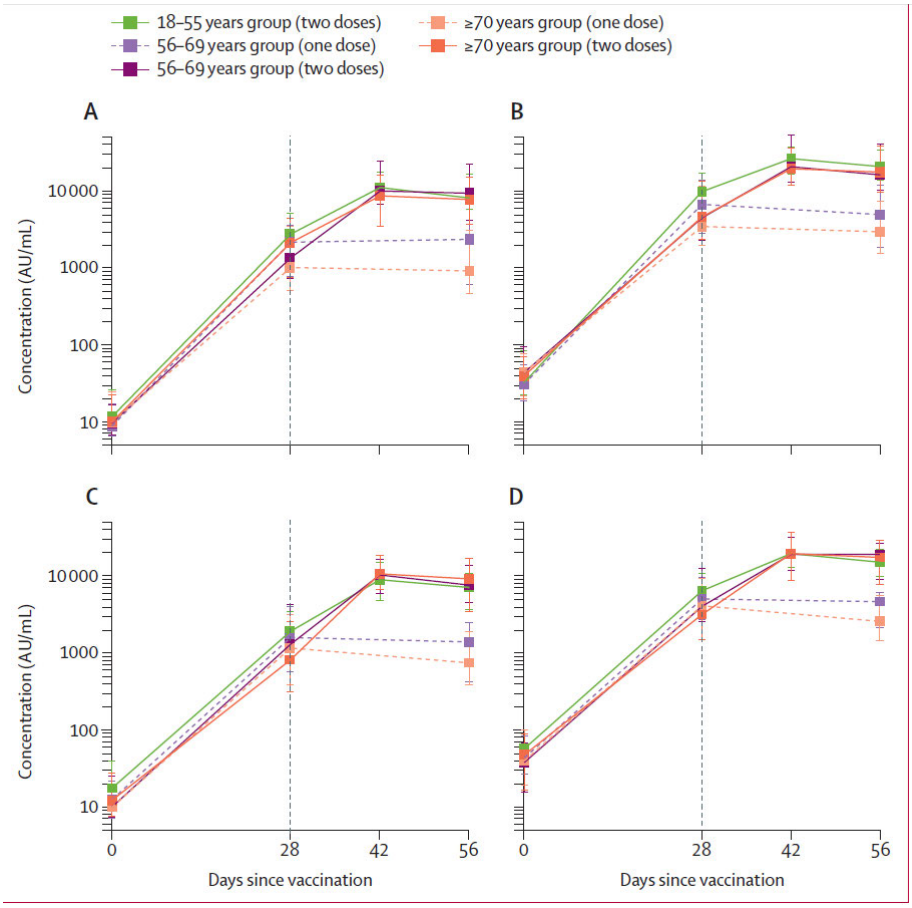

Figure 4: SARS-CoV-2 IgG response to the receptor binding domain in the standard-dose groups (A) and low-dose groups (C) and the spike protein in the standard-dose groups (B) and the low-dose groups (D), by age

Datapoints are medians, with whiskers showing the IQRs. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. The vertical black line indicates when participants who received two doses received their boost dose. Data for the control groups are shown in the appendix (p 12). AU=arbitrary units. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

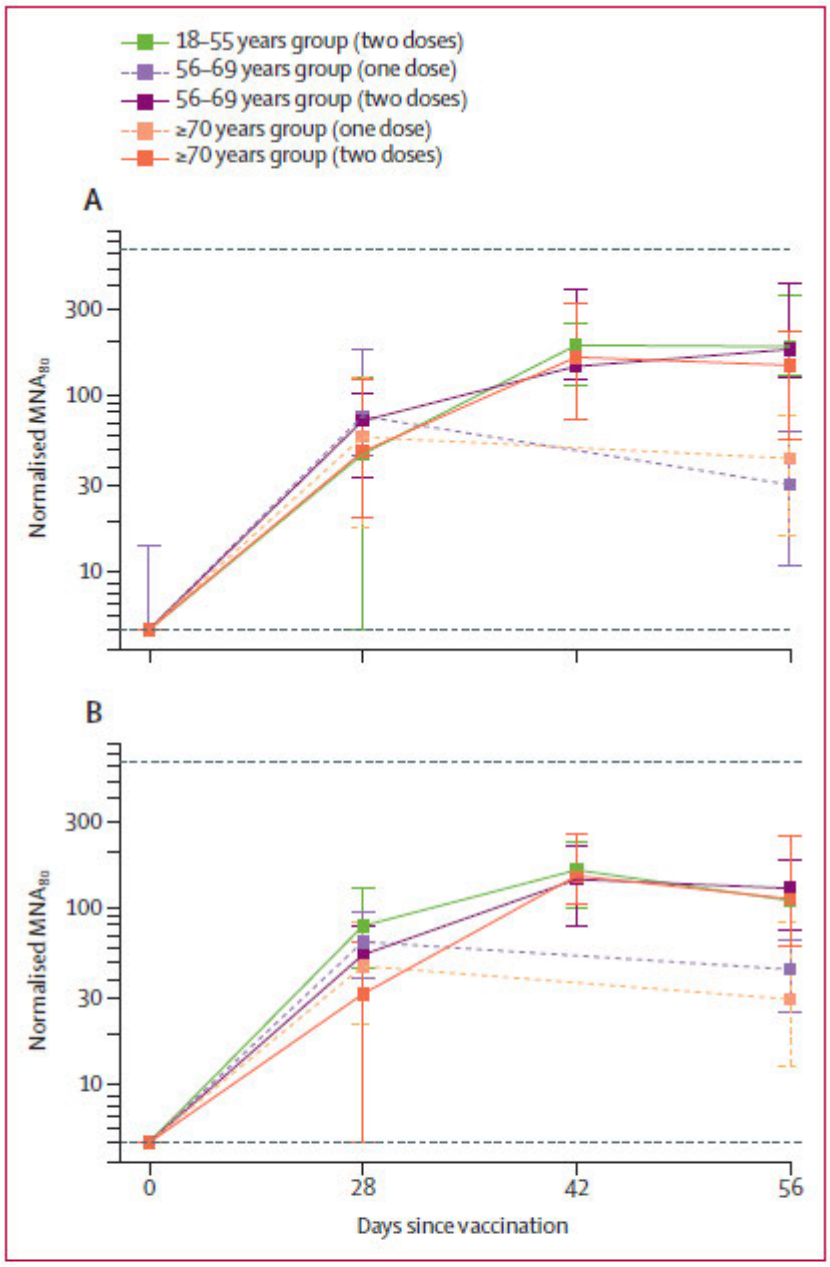

***Figure 5*: Neutralising antibody titres measured using a live SARS-CoV-2 microneutralisation assay (MNA_{80}) after prime and boost doses of vaccine in standard-dose groups (A) and low-dose groups (B), by age**

Datapoints are medians, with whiskers showing the IQR. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. Horizontal dotted lines show upper and lower limits of assay (values outside this range set to 640 beyond the upper limit and 5 beyond the lower limit). Data for the control groups are shown in the appendix (p 14).

To normalise data across assay runs, a reference sample was included in all assay runs and test samples normalised to this value by generating $\log_{10}$ ratios.

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

IFN-λ ELISpot response against SARS CoV-2 spike protein peaked at 14 days after the prime vaccination and did not increase significantly after the second dose (Figure 6).

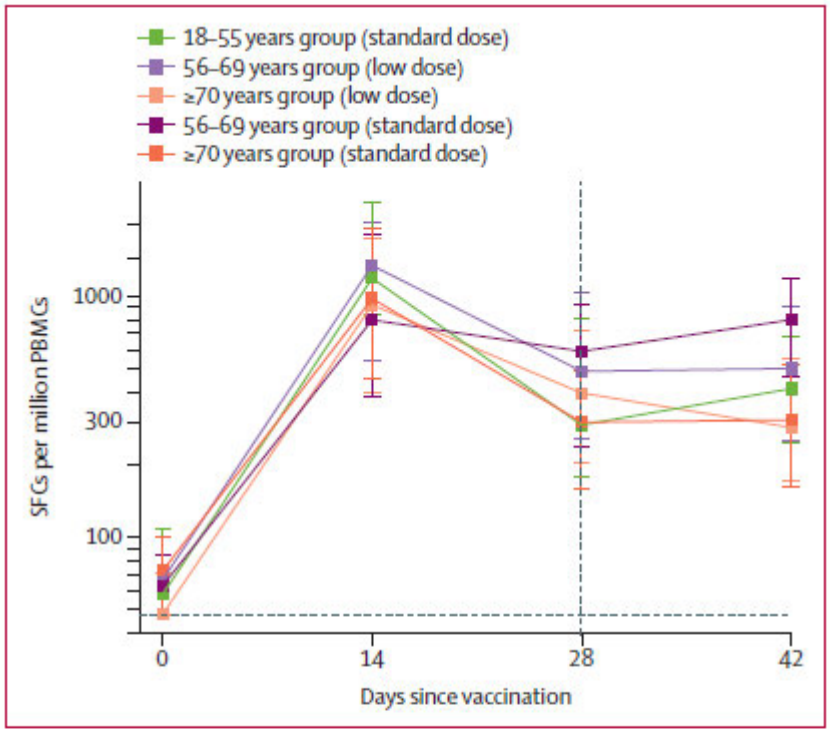

Figure 6: **IFN-γ ELISpot response to peptides spanning the SARS-CoV-2 spike insert after prime and boost doses of vaccine for all participants who were given two doses of vaccine, by age group and vaccine dose**

ELISpot data were unavailable for the 18–55 years low-dose group because PBMCs were not collected in this group. Datapoints are medians, with whiskers showing the IQR. The lower limit of detection is 48 SFCs per million PBMCs (horizontal dotted line). Day 42 samples are from participants who received the boost dose at day 28 (vertical dotted line). Data for both one-dose and two-dose groups, with numbers analysed at each timepoint, are in the appendix (p 15). ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

Anti vector antibodies increased after the initial dose and peaked on day 28. There was no further increase after the second dose. The titre of anti-vector antibodies did not appear to impact upon the titre of antibody to spike of RBD protein (Figure 7).

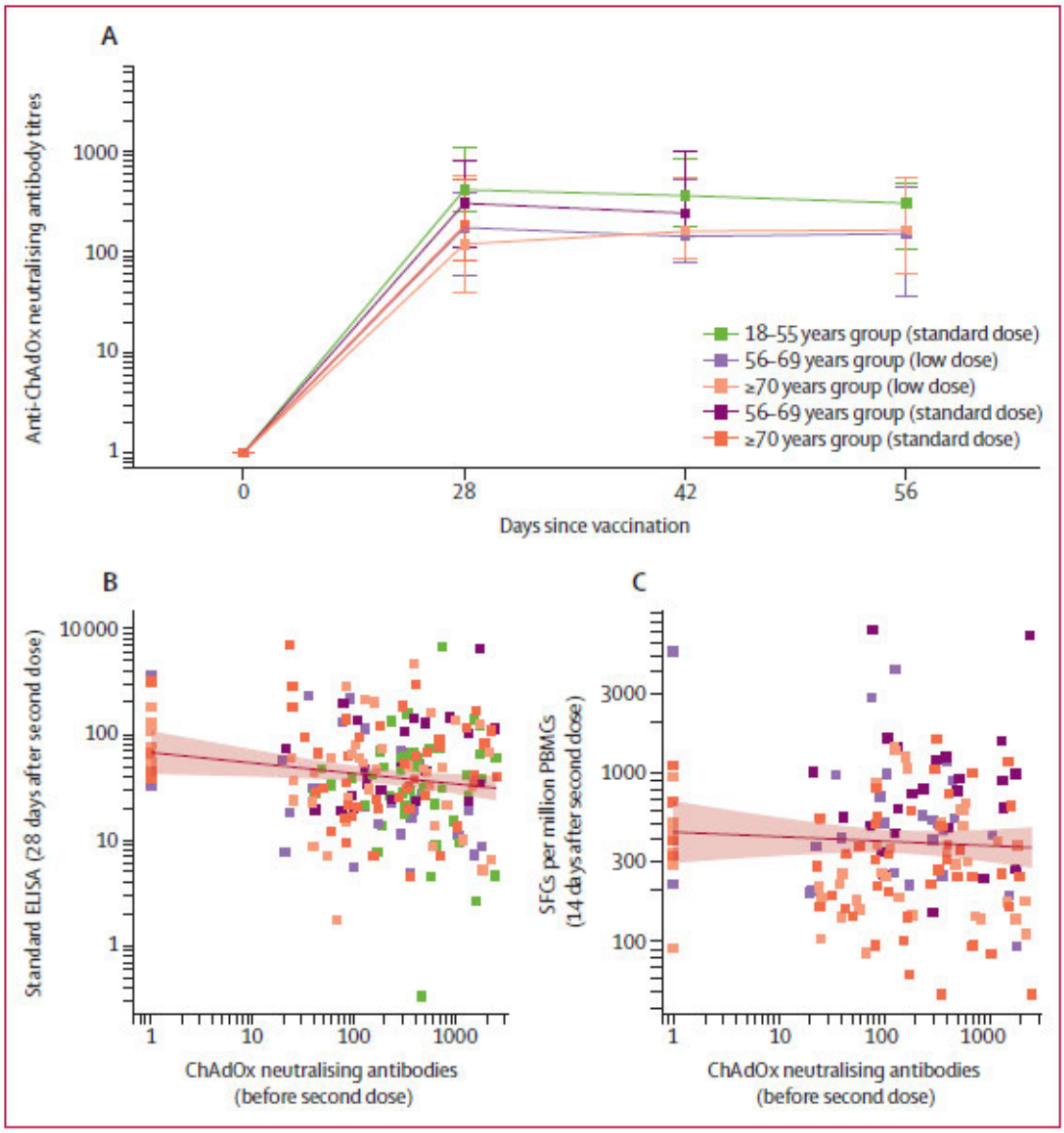

Figure 7: **Anti-ChAdOx1 vector neutralising titres after prime and boost doses of vaccine, by age and vaccine dose, and the correlation between pre-boost dose anti-ChAdOx1 neutralising antibodies and 28 days after boost dose antibody and T-cell responses**

(A) Anti-ChAdOx1 neutralising antibody titres in participants who received ChAdOx1 nCoV-19 vaccine by age and dose: datapoints are medians, with whiskers showing the IQR. Values below the limit of detection were assigned a value of 1. (B) Anti-ChAdOx1 neutralising antibody titre immediately before boost dose of vaccine versus standardised IgG ELISA against SARS-CoV-2 spike 28 days after the boost dose of vaccine with linear regression of logged values (p=0·037). (C) Anti-ChAdOx1 neutralising antibody titres immediately before boost dose of vaccine versus SARS-CoV-2 spike specific T cells measured by IFN-γ ELISpot on day 14 after the boost dose of vaccine with linear regression of logged values (p=0·22). In B and C, each datapoint is one participant and the solid line shows the linear regression, with the shaded area showing the 95% CI from an unadjusted linear regression of anti-vector neutralisation titres against logged ELISA (in B) or ELISpot (in C) response. Data were unavailable at day 56 for the 56–69 years standard-dose group. ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

13.1.2. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase ½, single blind, randomised controlled trial.

Felegatti PM; Ewer KJ, et al. Lancet August 15, 2020

This was a phase ½ study performed at 5 sites in the UK. Volunteers age 18-55 years were recruited by local advertisements. Participants at high risk of exposure were excluded.

Participants were randomly assigned to receive either ChAdOx1 nCoV-19 or MenACWY vaccine. The vaccine was manufactured by the clinical biomanufacturing facility at the University of Oxford, UK. The dose administered was 5 X 10^{10} viral particles. Recruitment was staggered and into groups.

Group 1 (the phase 1 component of the study) consisted of participants who had intensive early follow-up visits for safety and immunogenicity purposes at days 3, 7, 14, 28, and 56 after vaccination. Group 2 consisted of participants who had higher blood volumes drawn for humoral and cellular immunogenicity assessment than group 4, which consisted of participants who had a serum sample drawn for humoral immunology assessments only. Group 3 consisted of ten participants who were enrolled in a non-randomised prime-boost group and received a booster ChAdOx1 nCoV-19 administered 28 days after the first dose. These participants were not blinded and had extensive follow-up for safety and immunogenicity purposes, as per group 1, after each dose. A staggered enrolment approach was used for the first two, six, and 90 participants recruited in groups 1 and 3 and interim safety reviews with the independent Data and Safety Monitoring Board were done before proceeding with vaccinations in larger numbers of volunteers.

Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS CoV-2 spike protein, a multiplexed immunoassay (Meso Scale Discovery multiplexed immunoassay [MIA] against spike and receptor binding domain), three live SARS-CoV-2 neutralisation assays (Public Health England [PHE] plaque reduction neutralisation test [PRNT IC50], PHE micro neutralisation assay [MNA IC50, IC80, IC90], and Marburg virus neutralisation [VN IC100]), and a pseudovirus neutralisation assay (PseudoNA IC50). PHE PRNT is a live neutralisation assay and was done at PHE (Porton Down, UK). PHE MNA is a rapid microneutralisation assay, which was conducted in the same laboratory.

Convalescent plasma samples from adults (≥18 years) with PCR-positive SARS-CoV-2 infection were obtained from symptomatic patients admitted to hospital or from surveillance on health-care workers who did not have symptomatic infection. These samples were tested using standardised ELISA, MIA, PseudoNA, and Marburg VN. Different samples were analysed across the assays, dependent on sample availability, laboratory capacity, and assay-specific requirements. Where multiple longitudinal samples were available for the same participant, only one timepoint is included in the analyses and the earliest timepoint (at least 20 days after initial symptoms) was selected.

Results:

One thousand and seventy seven participants were enrolled in the study and assigned to vaccination the ChAdOx1 nCoV-19 or control. Of these, 10 received a booster dose.

Anti- spike, RBD and neutralising antibodies increased after this first dose until day 28. The antibody levels were similar, or slightly less, than those seen in convalescent plasma. The booster dose led to a further increase in antibody levels (figure 4 and 5). The peak T cell response occurred on day 14 and did not increase further after a booster dose.

Before vaccination, only one (1%) of 98 participants who were tested had high titre (>200) neutralising antibodies against ChAdOx1. Antibodies were detectable at a lower level in a further 18 (18%) participants, and in 79 (81%) participants there were no detectable anti ChAdOx1 antibodies.

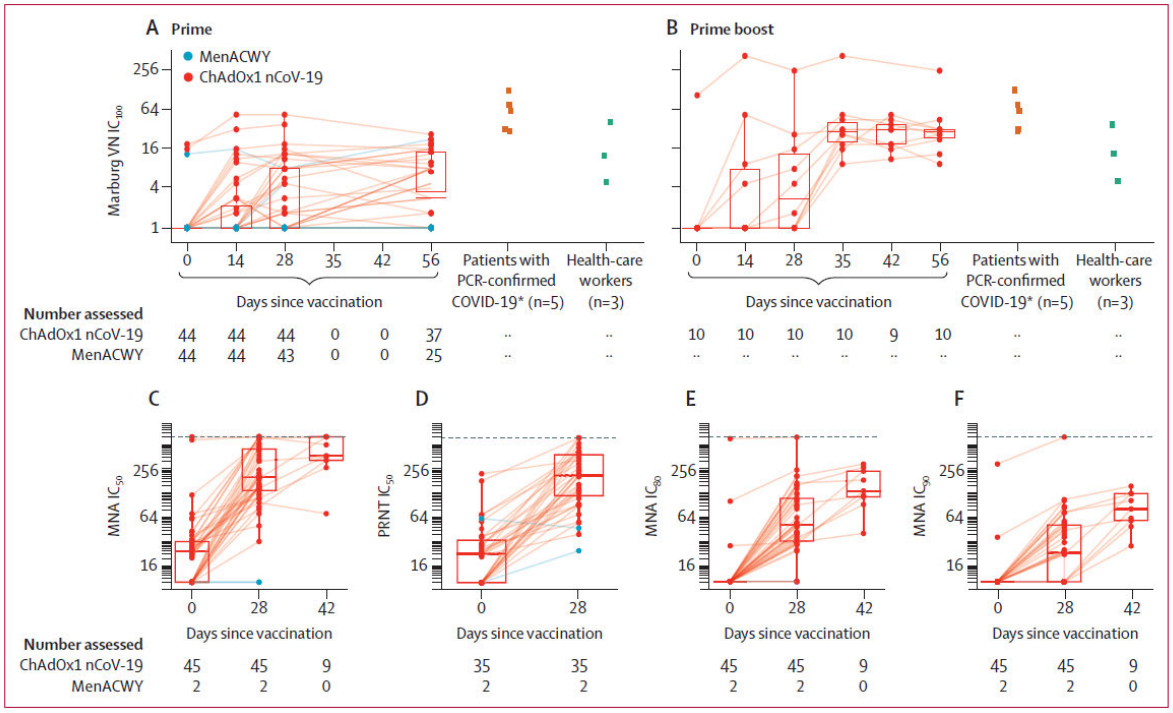

Figure 4: **Live SARS-CoV-2 neutralisation assays (Marburg VN and PHE $PRNT_{50}$) and microneutralisation assays (PHE MNA)**
Panels A and B show live SARS-CoV-2 neutralisation (Marburg VN) in prime (A) and prime boost (B) trial participants (boosted at day 28) and convalescent plasma from patients with PCR-confirmed COVID-19 and asymptomatic health-care workers. Panels C, E, and F show the PHE MNA (at IC_{50}, IC_{80}, and IC_{90}, respectively) and panel D the PHE $PRNT_{50}$. The day 42 timepoint was only measured in participants who received a booster dose at day 28. Solid lines connect samples from the same participant. Boxes show median (IQR). Dotted lines show upper limits of detection. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. PHE=Public Health England. MNA=microneutralisation assay. PRNT=plaque reduction neutralisation test. VN=virus neutralisation. IC=inhibitory concentration. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *ELISA results for these five convalescent plasma samples are shown in figure 3 as red stars.

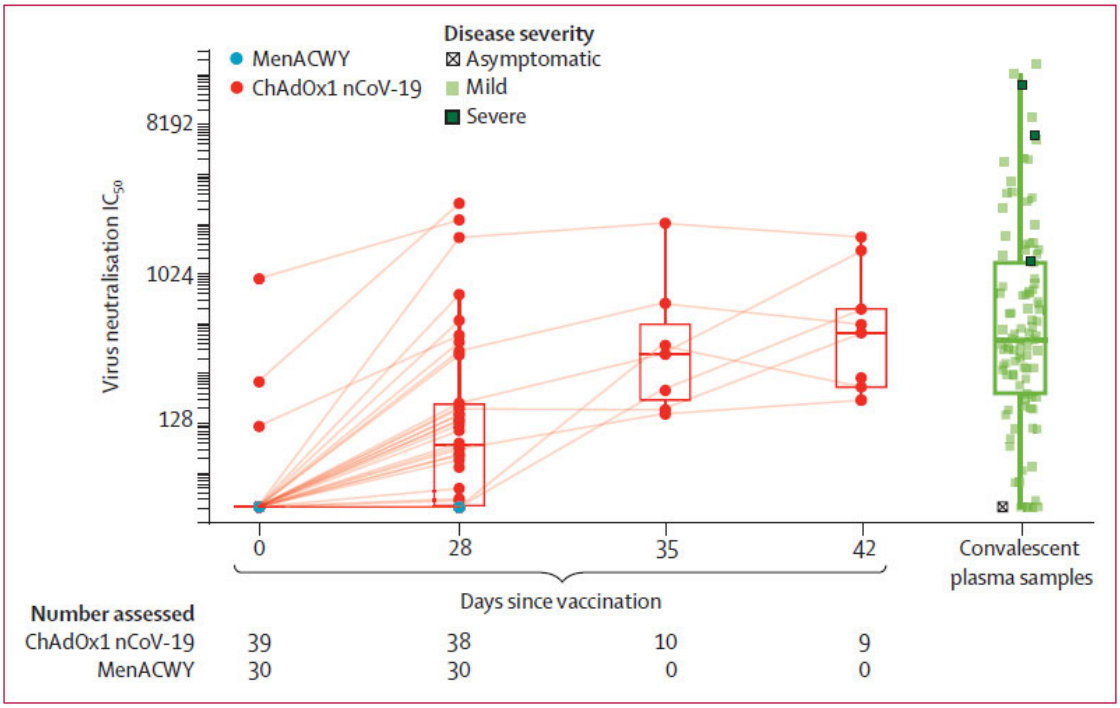

Figure 5: **PseudoNA results in trial participants and in convalescent plasma samples from 146 patients with PCR-confirmed COVID-19 and 24 asymptomatic health-care workers**
Solid lines connect samples from the same participant. Boxes show median (IQR). Results for days 35 and 42 are samples from participants who received a booster dose at day 28. IC=inhibitory concentration. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

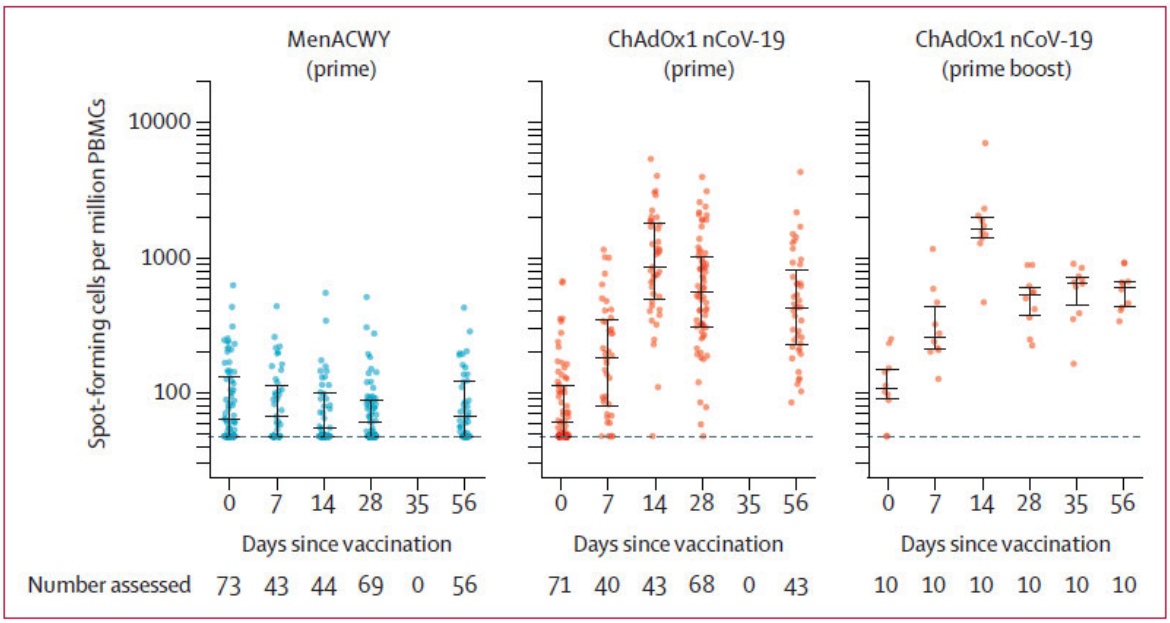

Figure 6: **Interferon-γ ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine insert**
Error bars show median (IQR). The lower limit of detection, indicated with the dotted line, is 48 spot-forming cells per million PBMCs. PBMC=peripheral blood mononuclear cell. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ELISpot=enzyme linked immunospot. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

13.1.3 T cell and antibody responses induced by a single dose of ChAdOx1nCoV-19 (AZD1222) vaccine in a phase ½ clinical trial

Ewer KJ, Barrett JR et al Nature Medicine (https://doi.org/10.1038/s41591-020-01194-5)

This is the same study population as that described in the paper by Folegatti.

Flow cytometric and combined t-distributed stochastic neighbour embedding (tSNE) analysis of 26 randomly selected ChAdOx1 nCoV-19 vaccinated volunteers showed discrete populations of T cells, natural killer cells and B cells. Within these clusters, there were distinct populations of proliferating (Ki-67+) or activating (CD69+) cells identified. IgG+ B cells upregulated Ki67 at all time points.

There was an increase in TNFα and IFNλ produced by CD4+ cells. Multiplex cytokine analysis after antigen specific stimulation of peripheral blood mononuclear cells with pooled SARS-CoV-2 spike peptide showed no increase in IL-β, IL-12p70, IL-4, IL-13 and IL-8.

Anti-SARS-CoV- IgG responses were detected day 14, peaked at day 28 and were maintained at day 56. Anti-SARS-CoV IgM and IgA peaked between days 14 and 28. Low SARS-CoV spike specific IgE was detected after vaccination, similar to that seen in convalescent plasma.

Anti-SARS-CoV spike specific IgG avidity increased significantly between day 28 and day 56. IgG avidity was similar to that seen in convalescent plasma after day 56.

The IgG subclasses were predominantly IgG3 and IgG1. Low levels of IgG2 and IgG4.

13.2. Study protocols of the studies in the meta-analysis

13.2.1. COV001 A phase I/II study to determine efficacy, safety and immunogenicity of COVID19 vaccine ChAdOx1CoV-19 in UK healthy adult volunteers

13.2.1.1. Study design, objectives, locations and dates

This was a single blinded, randomised, controlled, multi-centre study, based in the UK. The planned study duration is 12 months from the last vaccination visit. The date of first enrolment was 23rd April 2020. Patients from this study were included in the safety analysis and analysis of immunogenicity.

13.2.1.2. Inclusion and exclusion criteria

Healthy adults aged 18-55 years

Female participants were to be on contraception

The exclusion criteria were extensive and included (see section 18.2.2)

- Prior receipt of any vaccines < 30 days prior to enrolment, prior receipt of any vaccine likely to affect results (eg adenovirus vector vaccine or any coronavirus vaccine)
- Any confirmed or suspected immunosuppressive or immunodeficient state
- Autoimmune condition or allergic disease
- Any chronic physical condition including diabetes, asthma, heart disease, respiratory disease
- Seriously overweight
- History of laboratory confirmed COVID, or high risk of exposure
-

13.2.1.3. Study treatments

There were a number of different subgroups in this study

Table 42: Treatment schedule for groups in COV001

Group	Week 0	Week 4	Week 8
1a (n=44) Intense follow up	ChAdOx1CoV-19 $5X10^{10}$		
1b (n=44) Intense follow up	menACWY		
2a* (n< 206)	ChAdOx1CoV-19 $5X10^{10}$		
2b* (n<206)	menACWY		
2c* prime boost (up to 20 from 2a)	ChAdOx1CoV-19 $5X10^{10}$		ChAdOx1CoV-19 $5X10^{9}$
2d* prime boost (up to 32 from 2a)	ChAdOx1CoV-19 $5X10^{10}$		ChAdOx1CoV-19 2. $5X10^{9}$
2e* (up to 10 from 2b)	menACWY		menACWY
2f* (up to 154 from 2a)	ChAdOx1CoV-19 $5X10^{10}$	ChAdOx1CoV-19 3.5 to 6.5 $X10^{9}$	
2g* prime boost (up to 196 from 2b)	menACWY	menACWY	
3 (n=10) prime boost	ChAdOx1CoV-19 $5X10^{10}$	ChAdOx1CoV-19 $5X10^{9}$	
4a** (n= up to 290)	ChAdOx1CoV-19 $5X10^{9}$ panadol		
4b** (n=up to 290)	menACWY panadol		
4c **prime boost (n=up to 290)	ChAdOx1CoV-19 $5X10^{10}$ panadol	ChAdOx1CoV-19 3.5 to 6.5 $X10^{9}$	
4d** prime boost	menACWY	menACWY	

(n=up to 290)	panadol		

Both treatments were injected IM into the deltoid.

Vaccines for this study were manufactured at three different sites. These included the clinical biomanufacturing facility at the University of Oxford and Advent Sri Italy; or Cobra Biologics Ltd vialed at Symbiosis Pharmaceutical Services.

The control group received one of two MenACWY vaccine. The Nimenrix vaccine (Pfizer) is a single IM dose containing 5mcg each of Neisseria meningitides group A,C,W and Y polysaccharide, each conjugated to 44mcg tetanus toxoid carrier protein. The menveo (by Glaxo) contained 10mcg meningococcal A polysaccharide or 5mcg meningococcal polysaccharide C, W and Y conjugated to C.diphtheriae.

13.2.1.4. Efficacy variables and outcomes

Objectives and Outcome measures

Table 43: Objectives and Efficacy Outcomes for COV001

	Objective	**Outcome measure**
Primary	To assess efficacy of the ChAdOx1nCoV-19 against COVID-19	Virologically confirmed, symptomatic cases with COVID-19
Co-primary	To assess the safety of the ChAdOx1CoV-19	Occurrence of serious adverse events throughout the study duration
Secondary	To assess the safety, tolerability, and reactogenicity profile of the vaccine ChAdOx1nCoV	- Occurrence of local and systemic reactogenicity signs and symptoms for 7 days following vaccination - Occurrence of unsolicited adverse events for 28 days following vaccination - Change from baseline in safety laboratory measures - Occurrence of disease enhancement episodes
	To assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19	a) Hospital admissions associated with COVID-19 b) Intensive care unit (ICU) admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Severe COVID-19 disease (defined according to clinical severity scales). e) Seroconversion against non-Spike SARS-CoV-2 antigens
	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein; b) Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)

Blood tests for immunology parameters are taken at days 7, 14, 28, 56,182, 364 in group 1, days 28, 182 and 364 in groups 2a and 2b, days 28, 56, 14 days post boost, 28 days post boost, 182 days post boost, 362 days post boost

13.2.1.5. Randomisation and blinding methods

Participants in groups 1, 2 and 4 will be randomised. Randomisation will take place on a 1:1 ratio. Groups 1 and 3 will be the first to be recruited, followed by groups 2 and 4.

13.2.1.6. Sample size

Up to 1090

13.2.1.7. Statistical methods

Primary efficacy endpoint is a patient with positive PCR for COVID-19 and symptoms who were seronegative at baseline. An adjudication committee was used to confirm cases with symptomatic disease and severe disease.

Proportions will be compared between ChAdOx1 nCoV-19 and MenACWY groups using a Poisson regression model with robust variance. The logarithm of the period at risk for primary endpoint will be used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occur. Vaccine efficacy (VE) will be calculated as (1 – RR) x 100%, where RR is the relative risk of symptomatic infection (ChADOx1 nCoV-19: Control) and 95% confidence intervals will be presented.

Highly skewed antibody data will be log-transformed prior to analysis. The geometric mean concentration and associated 95% confidence interval will be summarised for each group at each timepoint, by computing the anti-log of the mean difference of the log-transformed data. The geometric mean concentration at day 28 and the proportion of participants seroconverting to the S-spike protein from day 0 to day 28 will be computed. Comparisons between ChAdOx1 nCoV-19 vaccine and MenACWY groups will be made using a Mann Whitney U test due to the low titres expected in the control group which will cause a non-normal distribution.

Spike-specific T cell responses (ELISpot) will be presented as means and confidence intervals, or medians and interquartile ranges if non-normally distributed at all post vaccination time points. Comparisons between ChAdOx1 nCoV-19 vaccine and MenACWY groups will be made using a Mann Whitney U test due to the low responses expected in the control group which will cause a non-normal distribution.

Subgroup comparisons of efficacy, and safety will be conducted by incorporating vaccine-group by subgroup interaction terms into appropriate regression models. Subgroup comparisons will only be conducted if there are at least 5 cases in all subgroups.
Comparisons will include:
1. Males vs females
2. Age (18 to 55 years vs 56-<70 years vs 70+ years)
3. Seropositive to S-spike or non-spike proteins at baseline vs not seropositive
4. Health care workers and highly-exposed participants versus others

It is planned that the primary evidence of efficacy and safety for the ChADOx1 nCoV-19 vaccine will be based on global analyses utilizing studies COV001 (the UK P1/2 study), COV002 (the UK P2/3 study), COV003 (the Brazil P3 study) and COV005 (the South Africa P1/2 study) including a pooled analysis across the studies.

Evidence of efficacy will be determined if the lower bound of the multiplicity adjusted confidence interval is greater than a 20% threshold. The primary analysis will have approximately 90% power assuming a vaccine efficacy of 60%.

13.2.1.8. Participant flow

See pooled results

13.2.1.9. Major protocol violations/deviations

Version 12 dated Nov 2020 was submitted in the dossier. The initial study protocol was written in March 2020.

Version 3: 23rd march 2020. Replace saline placebo with MenACWY.

Version 4: 20 April 2020. Addition of group 4. Change to statistical analysis. Reduced booster dose group 3 to 2.5X 1010vp.

Version 7: 19 May 2020. Booster dose changed back to 5 X 1010 as per study COV002.

Version 8: 22 June 2020. Added booster dose for subset of patients in group 2

Version 9: 30 June 2020. Added booster dose for all participants in groups 2 and 4.

13.2.2. COV002 A phase II/III study to determine efficacy, safety and immunogenicity of COVID19 vaccine ChAdOx1CoV-19

13.2.2.1. Study design, objectives, locations and dates

This was a single blinded, randomised, controlled, multi-centre study based in the UK. The planned study duration was 12 months from the last vaccination visit. The date of first enrolment was 29th May 2020. This study was used for analysis of efficacy, safety and immunogenicity.

13.2.2.2. Inclusion and exclusion criteria

The main efficacy trial was in health adults aged 18 years and older.

There were sequential age escalation and de-escalation immunogenicity sub studies

1. In health adults aged 56-70 years
2. Healthy adults aged 70 years and older
3. Healthy children aged 5-12 years
4. Healthy adults aged 18-55 years
5. HIV positive adults aged 18-55 years. (receiving antiretroviral therapy, with undetectable viral load and CD4 > 350 cells/ml

The exclusion criteria were similar to that of study CV001 (see section ..)except for the inclusion of patients with broader age groups and with a diagnosis of HIV as per the subgroups proposed.

13.2.2.3. Study treatments

The drug product for this study was produced from two sites:-

1. Advent Italy- the formulation is 1.2ml in a 3ml vial
2. Cobra/Symbiosis- the formulation is 5ml in a 10R vial

Table 44: Treatments for groups in study COV002

Group	vaccine	Number	age
1	a1) Single dose nCOV19 vaccine, $5x10^{10}$vp (Abs 260)*, OR a2) Single dose MenACWY	N=30 N=10	Adults 56-69 years

	a3) Two-dose nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL (3.5 -6.5 X 10^{10} vp, Abs 260 corrected for PS80 OR a4) Two-dose MenACWY, b1) Two dose nCOV19 vaccine, $5x10^{10}$vp (Abs 260) prime and $2.2x10^{10}$vp (qPCR) boost* (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=30 N=10 n-30 n=10	
2	a1) Single dose nCOV19 vaccine, $5x10^{10}$vp (Abs 260)*, OR a2) Single dose MenACWY (4-6 weeks apart) a3) Two-dose nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost*, OR a4) Two-dose MenACWY b1) Two dose nCOV19 vaccine, $5x10^{10}$vp (Abs 260) prime and $2.2x10^{10}$vp (qPCR) boost * (4-6 weeks apart), OR b2) Two-dose MenACWY	N=50 N=10 N=50 N=10 N=50 N=10 N=10	Adults over 70 years
3	Single dose nCoV-19 vaccine 2.5 X 10^{10} vp or MenACWY	N=30 N=30	Children aged 5-12 years
4	A1) single dose nCoV-19, 5 X 10^{10}vp A2) menACWY b1) Two dose nCOV19 vaccine, $5x10^{10}$vp (Abs260) prime and 2.2x1010vp (qPCR) boost* (4-6 weeks apart) OR b2) Two dose MenACWY c1) Two dose nCOV19 vaccine, $5x10^{10}$vp (Abs260) prime and 0.5mL (3.5 – 6.5 × 1010 vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost (at least 4 weeks apart) OR c2) Two dose MenACWY	1775 each group up to 50 each group 1725 each group	Adults aged 18-55 years
5	a1) Single dose nCoV19 vaccine, $5x10^{10}$vp, (Abs 260)* OR a2) MenACWY	50 each group	Adults 18-55 years Aim of this group was to assess the impact of

	a3) Two-dose nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost* a4) Two-dose MenACWY b1) Single dose nCoV19 vaccine, $5x10^{10}$vp, (qPCR)* OR b2) Men ACWY MenACWY (B-cell immunology only) c1) Single dose ChAdOx1 nCoV19 vaccine, $5x10^{10}$vp, (qPCR)* OR c2) MenACWY (B and T-cell im d1) Two-dose ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) OR d2) Men ACWY Immunology)	50 each group 25 each group 25 each group Up to 50 Up to 100	different manufacturing sites
6	a1) nCoV19 vaccine, $5x10^{10}$vp (qPCR)* OR a2) MenACWY b1) Two dose ChAdOx1 nCoV-19 vaccine, $5x10^{10}$vp (qPCR) prime and 0.5mL (3.5 – 6.5 × 1010 vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost* (at least 4 weeks apart) OR b2) Two dose MenACWY	up to 3000 each group Up to 3000 each group	Adults aged 18-55 years
7	a1) Single dose nCOV19 vaccine, $5x10^{10}$vp (qPCR)*, OR a2) Single dose MenACWY b1) Two dose nCOV19 vaccine, $5x10^{10}$vp (qPCR)* (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=30 N=10 N=30 N=10	Adults age 56-69 years
8	a1) Single dose nCOV19 vaccine, $5x10^{10}$vp (qPCR)*, OR a2) Single dose MenACWY b1) Two dose nCOV19 vaccine, $5x10^{10}$vp (qPCR) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=50 N=10 N=10	Adults aged 70 years and older
9	a1)Two dose nCOV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* (4-6 weeks apart) OR	About 500 each group	Adults age 56-69 years

	a2) Two dose MenACWY		
10	a1)Two dose nCOV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* (4-6 weeks apart) OR a2) Two dose MenACWY	About 500 each group	Adults aged 70 years and older
11	Two dose nCOV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* (4-6 weeks apart)	Up to 60	Adults 18-55 who have previously received ChAdOx1 vectored vaccine
12	Two dose ChAdOx1 nCOV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* (4-6 weeks apart)	Up to 60	HIV positive adults 18-55 years

Both treatments were injected IM

The control group received one of two MenACWY vaccine. The Nimenrix vaccine (Pfizer) is a single IM dose containing 5mcg each of Neisseria meningitides group A,C,W and Y polysaccharide, each conjugated to 44mcg tetanus toxoid carrier protein. The menveo (by Glaxo) contained 10mcg meningococcal A polysaccharide or 5mcg meningococcal polysaccharide C, W and Y conjugated to C.diphtheriae.

13.2.2.4. Efficacy variables and outcomes

Objectives and Outcome measures

Table 45: Objectives and outcome variables for study COV002

	Objective	**Outcome measure**
Primary	To assess efficacy of the ChAdOx1nCoV-19 against COVID-19 in adults aged 18 years and older	Virologically confirmed, symptomatic cases with COVID-19
Co-primary	To assess the safety of ChADOx1 nCoV-19 vaccine in adults and children	Occurrence of serious adverse events throughout the study duration
Secondary	To assess the safety, tolerability, and reactogenicity profile of the ChAdOx1nCoV	- Occurrence of local and systemic reactogenicity signs and symptoms for 7 days following vaccination - Occurrence of unsolicited adverse events for 28 days following vaccination - Change from baseline in safety laboratory measures

		- Occurrence of disease enhancement episodes
	To assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19	a) Hospital admissions associated with COVID-19 b) Intensive care unit (ICU) admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Severe COVID-19 disease (defined according to clinical severity scales). e) Seroconversion against non-Spike SARS-CoV-2 antigens
	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein; b) Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)
	To assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years and older	

Blood tests for immunology parameters are taken at days 7,14 ,28, 56, 182, 364 in group 1, days 28, 182 and 364 in groups 2a and 2b, days 28, 56, 14 days post boost, 28 days post boost, 182 days post boost, 362 days post boost

13.2.2.5. Randomisation and blinding methods

Enrolment into groups 1, 4, 5, and 6 will commence first. Then group 2. Recruitment into group 3 will commence when safety and immunogenicity data are reviewed from groups 1, 2 and 5. Recruitment into subsequent groups will follow.

Evaluator comment: Older patients were recruited later in the study protocol. This has implications in terms of the number of patients enrolled at the time of interim analysis, and also the duration of time available for follow up in this age group.

13.2.2.6. Analysis populations

Groups 1, 2, 5, 7, and 8 are designed to provide safety, reactogenicity, and immunogenicity data, as well as compare these data across AZD1222 batches made by different manufacturers. Groups 4, 6, 9 and 10 are the main groups for evaluating efficacy in each age group. Group 3 will evaluate safety and immunogenicity in children 5 to 12 years of age. Group 11 is an open-label and not randomised group to investigate the impact of previous ChAdOx1 vectored vaccines in immune responses elicited by AZD1222. Group 12 is a single arm group whereby up to 60 HIV infected individuals who are stable on antiretroviral therapy (ARV) will be recruited to receive 2 SD of AZD1222 4 to 6 weeks apart.

13.2.2.7. Sample size

Up to 12 390

13.2.2.8. Statistical methods

1. *Efficacy of two doses of vaccine* where the booster vaccine was a high-dose ChAdOx1 nCoV-19. Only participants who received two doses will be included (LD/SD or SD/SD) and only cases occurring more than 14 days after the second vaccine will be included.

Secondary analysis

2. *Efficacy of at least one standard-dose* of any ChAdOx1 nCoV-19. Cases occurring more than 21 days after the first vaccination will be included if the first vaccine was a high-dose vaccine. For participants who received a low-dose as their first vaccine, only cases occurring more than 14 days after a standard-dose booster will be included. Participants receiving only low-dose vaccines will be excluded.
3. *Efficacy of two standard-doses of vaccine.* Only participants who received two standard-dose vaccines will be included and only cases occurring more than 14 days after the second vaccine will be included.

Proportions will be compared between ChAdOx1 nCoV-19 and MenACWY using a Poisson regression model with robust variance. The logarithm of the period at risk for primary endpoint will be used as an offset variable in the model to adjust for volunteers having different follow up times.

Subgroup analyses

Subgroup comparisons of efficacy, and safety will be conducted by incorporating vaccine-group by subgroup interaction terms into appropriate regression models. Subgroup comparisons will only be conducted if there are at least 5 cases in all subgroups.

Comparisons will include:

1. Males vs females
2. Age (18 to 55 years vs 56-<70 years vs 70+ years)
3. Seropositive to S-spike or non-spike proteins at baseline vs not seropositive
4. Health care workers and highly-exposed participants versus others
5. Standard dose versus low dose

13.2.2.9. Participant flow

See pooled analysis

13.2.2.10. Major protocol violations/deviations

The submitted protocol was version 14, Nov 2020.

Version 1: 3rd April 2020

Version 4: 14 May 2020 : 1 year follow up as standard trial; add group 5 for batch safety and immunogenicity comparison to COV001; increased sample size to 10, 260; adjusted statistical analysis; add efficacy against infection as exploratory endpoint with weekly PCR testing.

Version 5: 26 May 2020: addition of age stratification in group 4 to < or > 55 years, removed need for baseline PCR swab;

Version 6: 5 Jun 2020 reduced participants in group 4, added group 6 to investigate comparison of dosing methods between Abs260 and qPCR

Version 7: 18 Jun 2020 addition of subgroups within groups 5, 7 and 8 to assess reactogeniticy and immunogenicity comparison between different doses given with different methods of measuring doses, increase sample size to 10 560; add subgroup 4b to assess the impact of a booster dose

Version 9: 20 July 2020 increased sample size, added group 5d (batch comparison to Cobra material), add groups 9 and 10 (efficacy in patients aged 56 years and above), added booster doses to groups 4 and 6, remove requirement for ChAdOx1 serology

Version 11: 15 September. Addition of boosting doses to groups 1a, 2a and 5a. Addition of HIV cohort substudy.

[redacted]

Table 46: Dose administered in COV002 study groups 4,6,9 and 10

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

Low dose: ≈$2.2x10^{10}$ and Standard dose $5.0x10^{10}$ vp,
A= Advent S= Symbiosis/Cobra

13.2.3. Study CV-003 A randomized, controlled, phase III study to determine the safety, efficacy and immunogenicity of the non replicating ChAdOx1nCoV-19 Vaccine.

13.2.3.1. Study design, objectives, locations and dates

This was a single blind, randomised study of safety, efficacy and immunogenicity based in Brazil. The planned treatment duration was 12 months post final vaccine dose. The date of first enrolment was June 2020. This study was used to assess efficacy, safety and immunogenicity in the pooled analysis.

There was a number of changes in protocol during this study (see 7.2.3.9).

13.2.3.2. Inclusion and exclusion criteria

Adult participants over the age of 18 will be enrolled in the study.
Recruitment will focus on healthcare professionals and those with likely high known exposure to COVID-19 (for example drivers, cleaning personnel, reception personnel). Participants over 55 will be recruited pending the investigators discretion

Exclusion criteria were the same as COV001.

13.2.3.3. Study Treatments

Both groups received prophylactic paracetamol.

Table 47: Study treatments for groups in study COV003

group	Vaccine	number	participants
1a	Single dose ChAdOx1nCOV19 vaccine,	Up to 1600	Health professionals and adults with high risk of exposure
1b	Single dose MenACWY	Up to 1600	Health professionals and adults with high risk of exposure

1c	Two doses ChAdOx1nCOV19 vaccine 4-12 weeks apart	Up to 5150	From 1 a and new participants
1d	Single dose MenACWY and saline placebo prime boost	Up to 5150	From 1b and new participants

Following the immunogenicity results of the UK phase I/II study which showed higher levels of neutralizing antibodies with a prime-boost schedule a booster dose of vaccine was offered to all participants in the study.
Participants enrolled on version 4.0 of the protocol onwards received 2 doses of either ChAdOx1 nCoV-19 or MenACWY/saline placebo. Participants who already received a dose of either ChAdOx1 nCoV-19 or MenACWY (before approvals for the second dose were in place) were offered a booster dose 4-12 weeks after the prime dose of either ChAdOx1 nCoV-19 or saline placebo, depending on which arm they were originally allocated to.

Patients in study groups 1a and 1b were seen at baseline, day 28, 90, 182 and 364. Patients in groups 1c and 1d were seen baseline, 4-12 weeks post prime, then day 28, 90, 182 and 364 post boost.

The COVID vaccines used in this study were from Advent, Italy, and Cobra Biologicals.

13.2.3.4. Efficacy variables and outcomes

Table 48: Objectives and efficacy endpoints for study COV003

	Objective	**endpoint**
Primary objective	To evaluate the efficacy of ChAdOx1 nCoV-19 vaccine against COVID-19 disease confirmed with PCR	COVID 19 virologically confirmed symptomatic cases (PCR positive)
Secondary objectives	To evaluate the safety, tolerability, and reactogenicity profile of ChAdOx1 nCoV-19 candidate vaccine.	a) Occurrence of signs and symptoms of local and systemic reactogenicity requested during 7 days after vaccination (in a subset of 200 participants*); b) Occurrence of serious adverse events; c) Occurrence of disease enhancement episodes .
	To evaluate the efficacy of ChAdOx1 nCoV- 19 candidate vaccine against severe and non-severe COVID-19 disease.	a) Hospitalization for COVID-19 disease confirmed by PCR; b) COVID-19 severe disease confirmed by PCR; c) Death associated with COVID-19 disease; d) Antibodies against SARS-CoV-2 non-Spike protein (efficacy against nonspike seroconversion rates).
	To assess the humoral immunogenicity of ChAdOx1 nCoV-19 candidate vaccine.	a) Antibodies against SARS-CoV-2 spike protein (sero-conversion rates). b) Virus neutralizing antibodies (NAb) against live and/or pseudotyped SARS-CoV-2 virus
	To assess the cellular immunogenicity of ChAdOx1 nCoV-19 candidate vaccine.	a) Interferon-gamma (IFN-γ) enzyme linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein;

13.2.3.5. Randomisation and blinding methods

Randomisation to the investigational product or MenACWY was in a 1:1 ratio using block randomisation of 4 participants. The participants but not the team administering the vaccine will be blinded.

13.2.3.6. Sample size

The planned sample size was up to 10 300 participants

13.2.3.7. Statistical methods

A primary efficacy analysis will be performed on all patients who are seronegative at baseline. Additional sensitivity analysis will be performed in all participants regardless of baseline serostatus.

Analysis of the primary endpoint will be computed as follows:
1. **Efficacy of two doses of ChAdOx1 nCoV-19**. Participants will be included who received two doses of ChAdOx1 nCoV-19. Events will be included if they occurred more than 14 days after the booster dose. Participants who are symptomatic up to 14 days after the second dose of vaccine will be excluded from the analysis. In addition, those with less than 14 days follow up post second dose will also be excluded.

Secondary analyses of the primary outcome:
2. **Efficacy of at least one dose of vaccine**. Cases occurring more than 21 days after the first vaccination will be included. Participants who are symptomatic up to 21 days from vaccination will still attend site for PCR testing and blood samples but will be excluded from the analysis as these participants may have been exposed to SARS-CoV-2 prior to vaccination or before the immune system has had time to mount a response to the vaccine. In addition, those with less than 21 days follow up post-vaccination will also be excluded.

13.2.3.8. Protocol amendments

The submitted protocol was version 8, dated November 2020

Version 1 was dated May 27th 2020

Version 4: July 28 2020. Added booster doses, removed requirement for negative COVID serology prior to enrolment, updated statistical analysis section,

Version 5: August 16 2020. Increased sample size to 10 000, changes to statistical analysis section including how the primary efficacy endpoint will be evaluated,

13.2.4. ChAdOx1 nCoV-19_ZA_ph1/11 CV 005: 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 with and without HIV, and safety and immunogenicity in adults living with HIV.

The date of first enrolment was Jun 2020. The study was used for safety and immunogenicity in the meta-analysis.

13.2.4.1. Study population:

Adults aged 18-65 years with and without HIV

Women were to have a negative pregnancy test at screening and be on a contraceptive

Patients with HIV need to have been on anti-retroviral treatment for at least 3 months and have a viral load of < 1000 copies per ml within 2 weeks of randomisation

The exclusion criteria were extensive (see later). They included use of any vaccine within the COVID vaccine, or involvement in any other COVID trials, any chronic disease (except stable endocrine disease), chronic respiratory disease, seriously overweight (BMI > 40kg/m2), symptoms of COVID or contact with COVID, confirmed or suspected immunodeficient or immunosuppressive state

13.2.4.2. Study treatments

The study involved 4 groups

Table 49: Study groups and treatment for COV005

groups	objective	Doses
1 N=70 People without HIV	Intensive safety and immunogenicity	2 doses, 21-35 days apart
2a N=250 People without HIV	Safety, intensive immunogenicity and vaccine efficacy	2 doses, 21-35 days apart
2b N=1650 People without HIV	Safety, intensive immunogenicity and vaccine efficacy	2 doses, 21-35 days apart
3 people with HIV	Intensive safety and immunogenicity	Prime boost 2 doses, 21-35 days apart

ChAdOx1 is administered by IMI injection in the deltoid. The vaccine for this study was manufactured at Cobra Biologics, UK; and Advent Italy.

Placebo is normal saline.

13.2.4.3. Endpoints/objective measures:

Table 50: Objectives and efficacy endpoints for COV005

Objective	Objective detail	measures
Co-primary	Safety, tolerability, reactogenicity profile	- Solicited local and systemic reactogenicity signs and symptoms for 7 days post vaccination - Unsolicited AEs 28 days post vaccination - Change in baseline for lab measures - SAE

		- Disease enhancements episodes
Co-primary efficacy	To assess efficacy of ChAdOx1 nCoV 19 against all severity COVID 19	Primary efficacy endpoint is PCR positive COVID disease cases in participants who were COVID-19 naïve more than 14 days after 2 doses Secondary efficacy endpoints were: a. Prevention of virologically confirmed COVID 19 clinical disease occurring 21 days after a single dose b. Prevention of virologically confirmed COVID 19 clinical disease in patients that were seropositive at baseline, more than 14 days after a second dose c. Prevention of PCR positive COVID cases d. Prevention of severe disease e. Prevention of hospitalisation f. Prevention of death g. Prevention of all cause LRTI
Secondary objective	Cellular and humoral immunogenicity	a) ELISA or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS CoV 2 spike protein b) Interferon gamma enzyme linked immunospot response to SARS CoV 2 spike protein c) Virus neutralising antibody assays against live and/or pseudotyped SARS CoV2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination

Immunological Assays

Ex vivo IFN gamma ELISpot assay	Used to quantify the frequency of antigen specific effector T cells in response to vaccination	Peptides are designed to cover the length of one of the SARS0CoV2 spike construct and comprise 15mer peptides
Cytokine analysis for IFNgamma and IL-2, other TH2 cytokines, and other proinflammatory markers such as TNF alpha	Using commercial kits	
Neutralisation assays	Pseudoneutralisation assay	

13.2.4.4. Randomisation:

In a 1:1 ratio in blocks of 8. Participants and clinical staff are blinded as to the treatment allocation. Site pharmacists and the person administering the vaccine will be not be blinded.

13.2.4.5. Statistics and study design

The sample size for group 2 were performed based on the total number of cases required to conclude with 80% power of at least 60% vaccine efficacy (with lower 95% CI over 0%) and an attach rate of 3.5% in the placebo group.

The per protocol analysis include all participants who receive 2 doses of study product where the second dose is more than 21 days after the first dose.

The primary efficacy endpoint is virologically confirmed COVID-19 clinical disease with a positive SARS CoV-2 RT-PCR swab.

The main efficacy population was those who were seronegative at baseline and received 2 doses of vaccine. The sensitivity analysis will be conducted using a modified ITT analysis.

Cumulative incidence will be reported by using the Kaplan Meier method.

Second efficacy analysis will examine the impact of AZ1222 in preventing the following endpoints both 14 days after the second dose and 21 days after the first dose.

- Virologically confirmed COVID clinical disease irrespective of COVID-19 sero-status at randomisation, and in those who were seropositive at randomisation
- VE in preventing PCR positive COVID-19 disease cases
- VE in preventing moderate-severe confirmed disease
- VE in preventing severe confirmed COVID disease
- VE in preventing LRTI associated virologically confirmed COVID-19 clinical disease
- VE in preventing hospitalisation due to virologically confirmed COVID-19 disease
- VE in preventing all-cause LRTI (overall and stratified by hospitalisation or not) irrespective of test result for SARS-COV-2
- VE using the oxford primary outcome definition

13.3. Other supporting tables and figures from the dossier

13.3.1. Inclusion and exclusion criteria in the meta-analysis

Table 31 Inclusion Criteria (Oxford-sponsored Clinical Studies to be Included in the Pooled Analyses for the MAA)

Inclusion Criterion	COV001	COV002	COV003	COV005
Adults aged 18-55 years	Yes	Yes	Yes	Yes
Adults aged 56 to 69 years	No	Yes	Yes	No
Adults aged 70 years and over [a]	No	Yes	Yes	No
Able and willing (in the Investigator's opinion) to comply with all study requirements	Yes	Yes	Yes	Yes
Willing to allow investigators to discuss the participant's clinical history with their general practitioner/personal physician and access medical records relevant to the study procedures	Yes	Yes	Yes	No
Willing to allow investigators to review available medical records, and review all medical and laboratory records if participant is admitted to hospital with respiratory tract infection suspected or confirmed to be COVID-19	No	No	No	Yes
Only for women of childbearing age willing to practice continuous effective birth control during the study, and a negative pregnancy test on the screening and vaccination day(s)	Yes	Yes	Yes	Yes
Agreement to refrain from blood donation during the course of the study	Yes	Yes	Yes	Yes
Provide written informed consent	Yes	Yes	Yes	Yes
Health professionals and adults at high risk of exposure to SARS-CoV-2	No	No	Yes	No
Serology with SARS-CoV-2 negative IgG antibodies	No	No	Yes [b]	No
HIV-Related				
For Study COV002 Group-12 (HIV sub-study): HIV positive; receiving anti-retroviral therapy; undetectable HIV viral load; CD4 > 350 cells/mL	No	Yes	No	No
For Study COV005 Groups 1 and 2 only: documented result of not being infected with HIV (including screening by a rapid HIV antibody test) within 2 weeks of randomisation	No	No	No	Yes
For Study COV005 Group 3 only (ie, HIV-infected), need to have been on anti-retroviral treatment for at least 3 months and HIV-1 viral load < 1000 copies/mL within 2 weeks of randomisation	No	No	No	Yes

[a] This age group was enrolled sequentially following the 56 to 69 years age group.
[b] For Study COV003: This inclusion criterion only applies to participants enrolled prior to protocol version 4.0.
Source: University of Oxford-sponsored study protocols for COV001 version 12.0, COV002 version 14.0, COV003 version 8.0, COV005 version 4.1

Table 32 Exclusion Criteria (Oxford-sponsored Clinical Studies to be Included in the Pooled Analyses for the MAA)

Exclusion Criterion	COV001	COV002	COV003	COV005
Medical Conditions				
Any autoimmune conditions, except mild psoriasis, well-controlled autoimmune thyroid disease, vitiligo, or stable coeliac disease not requiring immunosuppressive or immunomodulatory therapy	Yes	No	No	No
History of allergic disease or reactions likely to be exacerbated by any component of the AZD122 (or MenACWY, if applicable) vaccine	Yes	Yes	Yes	Yes
Any history of angioedema	Yes	Yes	Yes	Yes
Any history of anaphylaxis	Yes	Yes	Yes	Yes
Pregnancy, lactation, or willingness/intention to become pregnant during the study	Yes	Yes	Yes	Yes
Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)	No	Yes	Yes	No
History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)	Yes	Yes	Yes	Yes
History of serious psychiatric condition likely to affect participation in the study	Yes	Yes	Yes	Yes
Bleeding disorder	Yes	Yes	Yes	Yes
Continuous use of anticoagulants, such as coumarins and related anticoagulants (ie, warfarin) or novel oral anticoagulants (ie, apixaban, rivaroxaban, dabigatran, and edoxaban)	No	Yes	Yes	No
HbSAg positivity on the screening sample, or any sample obtained within three months of randomisation	No	No	No	Yes
Any other serious chronic illness requiring hospital specialist supervision	Yes	No	No	Yes
Chronic respiratory diseases, including mild asthma	Yes	No	No	Yes
Chronic cardiovascular disease (including hypertension), gastrointestinal disease, liver disease (except Gilberts Syndrome), renal disease, endocrine disorder (including diabetes), and neurological illness (excluding migraine)	Yes	No	No	No
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)	No	Yes	Yes	No
Seriously overweight (BMI ≥ 40 kg/m^2)	Yes	No	No	Yes

Exclusion Criterion	COV001	COV002	COV003	COV005
Seriously underweight (BMI ≤ 18 kg/m^2)	Yes	No	No	No
Alcohol or drug abuse	Yes	Yes	Yes	Yes
Suspected or known injecting drug abuse in the 5 years preceding enrolment	Yes	No	No	Yes
Any clinically significant abnormal finding on screening biochemistry or haematology blood tests	Yes	No	No	No
Any clinically significant abnormal finding on screening urinalysis	Yes	No	No	Yes
Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data	Yes	Yes	Yes	Yes
Chronic medical conditions such as chronic lung disease, chronic liver disease, chronic renal failure, chronic heart disease, congenital genetic syndromes (eg, Trisomy 21)	No	Group 3	No	No
Chronic disease inclusive of: a) Hypertension if ≥ Grade 2 based on DAIDS AE Grading Version 2.1-July 2017; b) Congestive heart failure; c) Chronic obstructive pulmonary disease by GOLD classification of ≥ 2; d) Evidence of coronary artery disease as manifested by cardiac interventions or cardiac medications for control of symptoms; e) Chronic type 2 diabetes (adult onset) requiring insulin; f) Chronic kidney disease/renal insufficiency; g) Chronic gastrointestinal and hepatic diseases; or h) Chronic neurological diseases	No	No	No	Yes
Grade 2 or higher level of abnormality for FBC, U&E, or LFT based on DAIDS Grading Criteria	No	No	No	Yes

Exclusion Criterion	COV001	COV002	COV003	COV005
Prior/Concomitant Therapy or Prior Clinical Study				
Prior receipt of any vaccines (licensed or investigational) ≤ 30 days before enrolment	Yes	No	Yes	No
Planned receipt of any vaccine other than the study intervention within 30 days before and after each study vaccination	Yes	Yes	Yes	Yes
Exception for seasonal influenza vaccine; participants encouraged to receive this vaccination at least 7 days before or after study vaccine	Yes	Yes	No	No
Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the study data	Yes	Yes [a]	Yes	Yes
Planned or ongoing participation in any other interventional studies (of licensed or investigational products) ≤ 30 days before enrolment and for the duration of the study	No	No	No	No
Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of study intervention	Yes	Yes	Yes	Yes
History of allergic disease or reactions likely to be exacerbated by paracetamol	Yes [b]	Yes [b]	Yes	No
COVID-19 Related				
History of laboratory-confirmed COVID-19	Yes	Yes	Yes	Yes
New onset of fever or a cough or shortness of breath or anosmia/ageusia since February 2020	Yes	No	No	No
New onset of fever or a cough or shortness of breath in the 30 days preceding screening and/or enrolment	No	No	No	Yes
High risk of exposure before enrolment	Yes	No	No	No
Living in the same household as any vulnerable groups at risk of severe COVID-19	Yes	No	No	No
Known close contact with a person that was infected with SARS-COV-2	No	No	No	Yes
Participation in COVID-19 prophylactic drug trials for the duration of the study [c]	No	Yes	Yes	No
Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study	No	Yes	No	No
Seropositivity to SARS-CoV-2 before enrolment	No	Yes	Yes [d]	No
Use of any unproven registered and unregistered treatments for COVID-19	No	No	No	Yes

13.3.2. Baseline Characteristics and Demographics of the efficacy population

Table 51: Baseline characteristics of the SDSD + LDSD seronegative efficacy analysis set

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	5799	5816	11615
	Mean	26.37	26.49	26.43
	SD	5.134	5.124	5.129
	Median	25.40	25.50	25.50
	Min	13.3	11.4	11.4
	Max	95.6	64.1	95.6
BMI category n (%)	< 30 kg/m2	4643 (80.0)	4619 (79.2)	9262 (79.6)
	>= 30 kg/m2	1156 (19.9)	1197 (20.5)	2353 (20.2)
	Missing	8 (0.1)	13 (0.2)	21 (0.2)
Serostatus at Day 0 n (%)	Negative	5807 (100)	5829 (100)	11636 (100)
Cardiovascular Disorder n (%)	Yes	639 (11.0)	602 (10.3)	1241 (10.7)
	No	5168 (89.0)	5227 (89.7)	10395 (89.3)
Chronic heart failure	Yes	0	1 (<0.1)	1 (<0.1)
Ischaemic heart disease (including angina)	Yes	8 (0.1)	8 (0.1)	16 (0.1)
Atrial fibrillation	Yes	13 (0.2)	15 (0.3)	28 (0.2)
Peripheral vascular disease	Yes	2 (<0.1)	3 (0.1)	5 (<0.1)
Valvular heart disease	Yes	8 (0.1)	15 (0.3)	23 (0.2)
Hypertension	Yes	306 (5.3)	279 (4.8)	585 (5.0)
Myocardial infarction	Yes	10 (0.2)	6 (0.1)	16 (0.1)
Other	Yes	157 (2.7)	143 (2.5)	300 (2.6)
Cardiovascular disorder with missing subcategory	Yes	135 (2.3)	132 (2.3)	267 (2.3)

Table 52: Demographics of the SDSD + LDSD seronegative efficacy analysis set

Characteristic	Statistics	AZD1222 (N =5807)	Control (N = 5829)	Total (N = 11636)
Race[a], n (%)	White	4807 (82.8)	4900 (84.1)	9707 (83.4)
	Asian	267 (4.6)	250 (4.3)	517 (4.4)
	Black	253 (4.4)	226 (3.9)	479 (4.1)
	Other	282 (4.9)	279 (4.8)	561 (4.8)
	Mixed	193 (3.3)	170 (2.9)	363 (3.1)
	Unknown	5 (0.1)	4 (0.1)	9 (0.1)
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 53: WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Table 54: Case definitions for evaluation of efficacy

Case	Definition
COVID-19 (Primary) Virologically-confirmed[a] symptomatic cases of COVID-19	PCR-confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.
COVID-19 Severe Disease	WHO grade ≥ 6[b]
COVID-19 Hospital Admission	WHO grade ≥ 4[b]
COVID-19 Requiring ICU	WHO grade ≥ 7[b]
COVID-19 Death	WHO grade = 10[b]
Asymptomatic SARS-CoV-2 infection	PCR-confirmed SARS-CoV-2 infection and not symptom record in data. Confirmed by adjudication committee.

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

Table 55: Overview of participants not receiving the second dose

	N(%) of participants			
	COV001 N=1067	**COV002 N=10663**	**COV003 N=10002**	**COV005 N=2013**
Participants that did not receive the second vaccination	268 (25.1)	2042 (19.2)	4941 (49.4)	179 (8.9)
Single dose group without second dose	88 (8.2)	191 (1.8)		
Participants had the second vaccination visit but vaccination form did not indicate complete	9 (0.8)	3 (<0.1)	8 (<0.1)	
Participants enrolled in the single dose group and have not responded to the optional second dose	142 (13.3)	585 (5.5)	2805 (28)	
Participants enrolled in the single dose group and declined the second dose	7 (0.7)	569 (5.3)	51 (0.5)	
Follow up < 12 weeks post first dose by 4th Nov	0	584 (5.5)	2032 (20.3)	159 (7.9)
Follow up > 12 weeks post first dose by 4th Nov	2 (2.1)	110 (1.1)	45 (0.4)	20 (1)

Table 56: Summary of solicited local adverse events collected with 7 days after vaccination by severity (pooled analysis dose 1 SD for safety analysis set)

Solicited Local AEs/ Severity		Days 0-7 After Any Vaccination		Days 0-7 After First Vaccination		Days 0-7 After Second Vaccination	
		AZD1222 n (%)	Control n (%)	AZD1222 n (%)	Control n (%)	AZD1222 n (%)	Control n (%)
Participants with any solicited local AE, n (%)	Total participants evaluated	2648	2497	2578	2423	1646	1518
	Any Severity	1979 (74.7)	1258 (50.4)	1839 (71.3)	1117 (46.1)	778 (47.3)	456 (30.0)
	1: Mild	1382 (52.2)	967 (38.7)	1317 (51.1)	894 (36.9)	614 (37.3)	357 (23.5)
	2: Moderate	345 (13.0)	153 (6.1)	312 (12.1)	111 (4.6)	94 (5.7)	61 (4.0)
	3: Severe	252 (9.5)	138 (5.5)	210 (8.1)	112 (4.6)	70 (4.3)	38 (2.5)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	941 (54.2)	586 (36.7)	889 (51.6)	512 (32.4)	221 (26.9)	169 (23.9)
	1: Mild	776 (44.7)	522 (32.7)	729 (42.3)	463 (29.3)	212 (25.8)	150 (21.2)
	2: Moderate	156 (9.0)	61 (3.8)	151 (8.8)	47 (3.0)	9 (1.1)	18 (2.5)
	3: Severe	9 (0.5)	3 (0.2)	9 (0.5)	2 (0.1)	0 (0.0)	1 (0.1)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tenderness, n (%)	Total participants evaluated	2648	2497	2577	2423	1644	1516
	Any Severity	1688 (63.7)	987 (39.5)	1555 (60.3)	866 (35.7)	638 (38.8)	361 (23.8)
	1: Mild	1398 (52.8)	902 (36.1)	1308 (50.8)	810 (33.4)	559 (34.0)	325 (21.4)
	2: Moderate	258 (9.7)	78 (3.1)	225 (8.7)	52 (2.1)	66 (4.0)	32 (2.1)
	3: Severe	32 (1.2)	7 (0.3)	22 (0.9)	4 (0.2)	13 (0.8)	4 (0.3)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Redness, n (%)	Total participants evaluated	2626	2480	2547	2394	1603	1471
	Any Severity	368 (14.0)	218 (8.8)	310 (12.2)	182 (7.6)	114 (7.1)	54 (3.7)
	1: 2.5 - 5 cm	176 (6.7)	123 (5.0)	159 (6.2)	106 (4.4)	46 (2.9)	32 (2.2)
	2: 5.1-10 cm	67 (2.6)	36 (1.5)	51 (2.0)	26 (1.1)	29 (1.8)	11 (0.7)
	3: > 10 cm	125 (4.8)	59 (2.4)	100 (3.9)	50 (2.1)	39 (2.4)	11 (0.7)
	4: Necrosis or ED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Warmth, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	308 (17.7)	232 (14.5)	272 (15.8)	199 (12.6)	71 (8.6)	64 (9.1)
	1: Mild	301 (17.3)	223 (14.0)	266 (15.4)	193 (12.2)	70 (8.5)	61 (8.6)
	2: Moderate	7 (0.4)	9 (0.6)	6 (0.3)	6 (0.4)	1 (0.1)	3 (0.4)
	3: Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Itch, n (%)	Total participants evaluated	2648	2497	2577	2422	1644	1516
	Any Severity	335 (12.7)	187 (7.5)	267 (10.4)	141 (5.8)	139 (8.5)	67 (4.4)
	1: Mild	272 (10.3)	156 (6.2)	221 (8.6)	121 (5.0)	114 (6.9)	54 (3.6)
	2: Moderate	53 (2.0)	26 (1.0)	40 (1.6)	16 (0.7)	19 (1.2)	12 (0.8)
	3: Severe	10 (0.4)	5 (0.2)	6 (0.2)	4 (0.2)	6 (0.4)	1 (0.1)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling, n (%)	Total participants evaluated	2626	2481	2547	2394	1602	1472
	Any Severity	262 (10.0)	145 (5.8)	216 (8.5)	114 (4.8)	87 (5.4)	44 (3.0)
	1: 2.5 - 5 cm and no IwA	96 (3.7)	52 (2.1)	83 (3.3)	37 (1.5)	32 (2.0)	22 (1.5)
	2: 5.1 - 10 cm or IwA	28 (1.1)	26 (1.0)	20 (0.8)	21 (0.9)	15 (0.9)	6 (0.4)
	3: > 10 cm or PDA	138 (5.3)	67 (2.7)	113 (4.4)	56 (2.3)	40 (2.5)	16 (1.1)
	4: Necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Induration, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	164 (9.4)	136 (8.5)	145 (8.4)	108 (6.8)	29 (3.5)	42 (5.9)
	1: 2.5 - 5 cm and no IwA	66 (3.8)	52 (3.3)	59 (3.4)	41 (2.6)	12 (1.5)	17 (2.4)
	2: 5.1 - 10 cm or IwA	27 (1.6)	27 (1.7)	21 (1.2)	21 (1.3)	9 (1.1)	9 (1.3)
	3: > 10 cm or PDA	71 (4.1)	57 (3.6)	65 (3.8)	46 (2.9)	8 (1.0)	16 (2.3)
	4: Necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bruising, n (%)	Total participants evaluated	912	901	855	844	821	809
	Any Severity	158 (17.3)	60 (6.7)	114 (13.3)	39 (4.6)	75 (9.1)	30 (3.7)
	1: <10 mm	123 (13.5)	48 (5.3)	88 (10.3)	30 (3.6)	59 (7.2)	26 (3.2)
	2: 10 - 25 mm	28 (3.1)	8 (0.9)	23 (2.7)	5 (0.6)	12 (1.5)	3 (0.4)
	3: > 25 mm	7 (0.8)	4 (0.4)	3 (0.4)	4 (0.5)	4 (0.5)	1 (0.1)

Table 57: Summary of systemic solicited adverse events collected within 7 days after vaccination: pooled analysis (Dose 1SD for safety analysis set)

		Number (%) of Participants					
		Days 0-7 After Any Vaccination		Days 0-7 After First Vaccination		Days 0-7 After Second Vaccination	
		AZD1222 n (%)	Control n (%)	AZD1222 n (%)	Control n (%)	AZD1222 n (%)	Control n (%)
Participants with any systemic solicited AE, n (%)	Total participants evaluated	2648	2497	2580	2424	1661	1526
	Any Severity	1932 (73.0)	1488 (59.6)	1817 (70.4)	1320 (54.5)	741 (44.6)	545 (35.7)
	1: Mild	973 (36.7)	1022 (40.9)	961 (37.2)	951 (39.2)	525 (31.6)	383 (25.1)
	2: Moderate	738 (27.9)	403 (16.1)	664 (25.7)	328 (13.5)	179 (10.8)	135 (8.8)
	3: Severe	220 (8.3)	63 (2.5)	191 (7.4)	41 (1.7)	37 (2.2)	27 (1.8)
	4: ER or hospitalisation	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever, n (%) *	Total participants evaluated	2644	2493	2558	2403	1644	1516
	Any Severity	208 (7.9)	31 (1.2)	189 (7.4)	21 (0.9)	21 (1.3)	13 (0.9)
	1: 38.0 - 38.4°C	122 (4.6)	18 (0.7)	113 (4.4)	12 (0.5)	11 (0.7)	8 (0.5)
	2: 38.5 - 38.9°C	67 (2.5)	6 (0.2)	59 (2.3)	5 (0.2)	8 (0.5)	2 (0.1)
	3: 39.0 - 40°C	18 (0.7)	7 (0.3)	16 (0.6)	4 (0.2)	2 (0.1)	3 (0.2)
	4: > 40°C	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feverishness, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	583 (33.6)	171 (10.7)	546 (31.7)	139 (8.8)	79 (9.6)	40 (5.7)
	1: Mild	270 (15.6)	153 (9.6)	246 (14.3)	127 (8.0)	62 (7.5)	33 (4.7)
	2: Moderate	252 (14.5)	16 (1.0)	241 (14.0)	11 (0.7)	15 (1.8)	6 (0.8)
	3: Severe	61 (3.5)	2 (0.1)	59 (3.4)	1 (0.1)	2 (0.2)	1 (0.1)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chills, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	554 (31.9)	132 (8.3)	535 (31.1)	108 (6.8)	42 (5.1)	32 (4.5)
	1: Mild	278 (16.0)	115 (7.2)	265 (15.4)	95 (6.0)	32 (3.9)	26 (3.7)
	2: Moderate	216 (12.4)	17 (1.1)	212 (12.3)	13 (0.8)	8 (1.0)	6 (0.8)
	3: Severe	60 (3.5)	0 (0.0)	58 (3.4)	0 (0.0)	2 (0.2)	0 (0.0)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pains, n (%)	Total participants evaluated	2648	2496	2577	2421	1645	1515
	Any Severity	698 (26.4)	310 (12.4)	619 (24.0)	234 (9.7)	168 (10.2)	109 (7.2)
	1: Mild	492 (18.6)	250 (10.0)	440 (17.1)	191 (7.9)	127 (7.7)	89 (5.9)
	2: Moderate	176 (6.6)	48 (1.9)	154 (6.0)	36 (1.5)	35 (2.1)	15 (1.0)
	3: Severe	30 (1.1)	12 (0.5)	25 (1.0)	7 (0.3)	6 (0.4)	5 (0.3)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle pains, n (%)	Total participants evaluated	2648	2496	2577	2422	1645	1515
	Any Severity	1164 (44.0)	540 (21.6)	1048 (40.7)	448 (18.5)	318 (19.3)	162 (10.7)
	1: Mild	797 (30.1)	452 (18.1)	732 (28.4)	389 (16.1)	250 (15.2)	130 (8.6)
	2: Moderate	317 (12.0)	79 (3.2)	275 (10.7)	53 (2.2)	59 (3.6)	29 (1.9)
	3: Severe	50 (1.9)	9 (0.4)	41 (1.6)	6 (0.2)	9 (0.5)	3 (0.2)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue, n (%)	Total participants evaluated	2648	2497	2577	2423	1646	1517
	Any Severity	1407 (53.1)	955 (38.2)	1295 (50.3)	821 (33.9)	457 (27.8)	308 (20.3)
	1: Mild	856 (32.3)	704 (28.2)	812 (31.5)	618 (25.5)	331 (20.1)	234 (15.4)
	2: Moderate	466 (17.6)	224 (9.0)	414 (16.1)	184 (7.6)	108 (6.6)	65 (4.3)
	3: Severe	85 (3.2)	27 (1.1)	69 (2.7)	19 (0.8)	18 (1.1)	9 (0.6)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache, n (%)	Total participants evaluated	2648	2497	2577	2423	1646	1517
	Any Severity	1394 (52.6)	975 (39.0)	1270 (49.3)	828 (34.2)	443 (26.9)	324 (21.4)
	1: Mild	901 (34.0)	743 (29.8)	842 (32.7)	665 (27.4)	343 (20.8)	235 (15.5)
	2: Moderate	422 (15.9)	209 (8.4)	368 (14.3)	149 (6.1)	85 (5.2)	77 (5.1)
	3: Severe	71 (2.7)	23 (0.9)	60 (2.3)	14 (0.6)	15 (0.9)	12 (0.8)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	768 (44.2)	323 (20.2)	703 (40.8)	265 (16.8)	147 (17.9)	80 (11.3)
	1: Mild	417 (24.0)	252 (15.8)	375 (21.8)	215 (13.6)	108 (13.1)	57 (8.1)
	2: Moderate	285 (16.4)	64 (4.0)	268 (15.6)	46 (2.9)	32 (3.9)	20 (2.8)
	3: Severe	66 (3.8)	7 (0.4)	60 (3.5)	4 (0.3)	7 (0.9)	3 (0.4)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	380 (21.9)	209 (13.1)	348 (20.2)	174 (11.0)	69 (8.4)	56 (7.9)
	1: Mild	291 (16.8)	173 (10.8)	264 (15.3)	150 (9.5)	60 (7.3)	44 (6.2)
	2: Moderate	74 (4.3)	34 (2.1)	72 (4.2)	23 (1.5)	6 (0.7)	11 (1.6)
	3: Severe	15 (0.9)	2 (0.1)	12 (0.7)	1 (0.1)	3 (0.4)	1 (0.1)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting, n (%)	Total participants evaluated	1736	1596	1722	1578	823	707
	Any Severity	29 (1.7)	14 (0.9)	24 (1.4)	12 (0.8)	5 (0.6)	3 (0.4)
	1: Mild	14 (0.8)	8 (0.5)	11 (0.6)	7 (0.4)	3 (0.4)	2 (0.3)
	2: Moderate	9 (0.5)	4 (0.3)	9 (0.5)	4 (0.3)	0 (0.0)	0 (0.0)
	3: Severe	6 (0.3)	2 (0.1)	4 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)
	4: ER or hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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