Australian Government
Department of Health
Therapeutic Goods Administration

# Delegate's overview

Active ingredient(s): ChAdOx1-S

Proprietary product name: COVID-19 vaccine Astra Zeneca

Sponsor: Astra Zeneca

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

eID : e005766

**28th th January 2021**

TGA Health Safety Regulation

# Submission information

| | |
|---|---|
| **Submission number** | PM-2021-06115-1-2 |
| **Active ingredient(s)** | ChAdOx1-S |
| **Product name** | COVID-19 Vaccine Astra Zeneca |
| **Strengths/dose form** | 1 X $10^{11}$ vp/ml multidose vial |
| **Sponsor** | Astra Zeneca |
| **Description of the submission/proposed indication** | The Sponsor proposes to register a new therapeutic entity with the following indication:<br>*" COVID-19 Astra Zeneca is indicated for active immunisation of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19)* |
| **Summary of data** | *The sponsor has submitted an interim analysis of a meta-analysis of 4 clinical studies. Over 23 000 subjects are available for the analysis of safety, around 10 000 are available for the analysis of efficacy.*<br>*There were a number of changes in the protocol during the clinical study, which has led to significant heterogeneity and potential confounding factors.*<br>*In addition, there was limited follow up time; high risk populations such as the elderly and those with significant co-morbidities were under-represented in the studies.*<br>*Dosing interval varied from 3 to 26 weeks.*<br>*For the dose proposed for registration, the SDSD group, efficacy was 62%.*<br>*Apart of reactogenicity, there were no significant safety concerns.* |
| **Preliminary view** | While a decision is yet to be made, at this stage I am inclined to approve the registration of the product.<br>If registration was approved, I would propose the following additional conditions of registration:<br>Quality:<br>TBA depending on what data is submitted within the next few weeks.<br>Section 14 exemption is required regarding labelling<br>Nonclinical:<br>To provide the following clinical studies to the TGA when they are available<br>1. The ongoing distribution study with AZD1222 |

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| | 2. The ongoing reproductive toxicity with AZD1222<br><br>Clinical:<br><br>1. Changes to the product information<br>2. That the sponsor provide the full study reports of COV001, COV002, COV003 and COV005 when available in 2022.<br>3. That the sponsor provide the interim and full study report for D8110COV00001<br>4. That the studies in the PV plan be included in the clinical study plan and be submitted prior to full registration<br><br>RMP:<br><br>To be confirmed but will include<br><br>- Monthly safety updates<br>- Submission of studies in the pharmacovigilance plan<br>- Inclusion of use in the elderly and long term safety in the missing information section of the summary of safety concerns |
| **Outstanding issues** | |

## Questions for the sponsor

1. When the studies included in the pharmacovigilance are plan due to be completed? Are they expected to be submitted to the TGA prior to full registration (ie within 6 years).
2. Please clarify if there will be ongoing studies in relation to the dosing interval

## Independent expert advice

| | |
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| **Summary of issue/s for advice/Advice sought** | Statistical report |
| **Advice received** | The statistician considered it appropriate to exclude the studies where there were < 5 cases of COVID-19.<br><br>He considered that Poisson models were appropriate, and that there would be very little gained from using Bayesian statistics.<br><br>The short duration of follow up, and decreasing number of participants followed as duration from the baseline increases, decreases the precision of data with longer duration of follow up. The Kaplan Meier curves were therefore misleading.<br><br>Statistical analysis of secondary or supportive endpoints should be considered cautiously, with the following factors considers 1) biological rationale for the subgroup; 2) prior evidence or belief that a differential effect in a subgroup is plausible 3) independent confirmation from other factors |

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| | in the study of the possible differential treatment effect in the subgroup |

## Request for ACV advice

**ACV meeting number: 19** **Date 3rd February**

| **Summary of issue/s for advice** | |
|---|---|
| **Advice sought** | 1. Depending upon which efficacy population is used, vaccine efficacy in 50-70%, with the lower 95% confidence interval over 40%, to prevent symptomatic COVID-19 infection. This complies with the EMA guidelines. The initial aims of the Australian Immunisation Program are to protect the high risk groups of the population. Do you consider this level of coverage acceptable for the aims of the Australian Immunisation Program.<br><br>2. Please comment on use in the elderly in view of the limited numbers available in the efficacy and safety analysis, and limited duration of follow up. Please review the wording of the PI in relation to use in the elderly and advise if there is a need for stronger wording or a limitation to ages in the indication.<br><br>3. In post hoc secondary subgroup analysis, great immunogenicity and efficacy was observed with longer dose intervals. Is there a scientific rational for this?<br><br>4. The dosing interval proposed by the sponsor is 4-12 weeks. From a regulatory perspective, this is satisfactory. Should information about efficacy of a single dose or efficacy by stratified dosing interval be included in the PI?<br><br>5. The pregnancy category is B2. Only one study has been performed in mice. Another study is ongoing. No abnormal findings were identified in the completed study. There were a small number of pregnant women exposed in the clinical study, but outcomes of pregnancy though are unknown. Currently the use in pregnancy section states " use in pregnancy is not recommended" . Is this adequate? |

[redacted]

28th January 2021

Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990
*Medical Officer 5, PMAB*

Date

# Body of overview

## Background

### Condition

In December 2019, a cluster of patients with pneumonia of unknown cause was discovered in Wuhan, China, and the patients were confirmed to be infected with the novel coronavirus now known as SARS-CoV-2. The WHO declared the novel coronavirus a pandemic on 11 March 2020. As of the 10th January 2021, there have been 88 387 351 cumulative cases, and 19 919 204 cumulative deaths worldwide.

Although most cases are mild or moderate in severity, severe disease can result in respiratory, multiorgan failure and death. Vulnerable groups for severe infection include the elderly, and those with co-morbidities including cardiovascular disease, respiratory disease and type 2 diabetes.

### Current treatment options

The management of COVID-19 disease is largely supportive. The only medication approved for use for the management of COVID-19 in remdesivir. Dexamethasone can be used in severely ill patients to reduce the number of ICU days and death.

Public health measures to reduce the spread of the disease has been the main strategy to manage the pandemic. This has involved social distancing, use of masks, border closures, restricting overseas travel, and hand washing. When used well this is affective, however at significant economic and social disruption. Many experts have stated that vaccination is the only way out of this pandemic.

There are currently a number of vaccine candidates in development. The TGA approved the Pfizer/Biotec vaccine in January 2021.

The world will require a number of different vaccines to control the pandemic as no one vaccine will be able to be manufactured in sufficient quantity to provide coverage for the world.

The Australian Government has been developing a roll out strategy in collaboration with a number of other organisations including the vaccination task force and ATAGI. The initial priority will be to vaccinate the high risk groups (high risk for infection, or severe infection or transmission).

### Australian regulatory status

This is a submission for provisional registration.

Note: Australia has secured 53.8 million doses of this vaccine. 3.8 million doses will be delivered to Australian in early 2021. 50 million doses will be manufactured in Australia by CSL.

Australian is a member of COVAX.

### International regulatory status

This vaccine has been authorized for temporary supply by the MHRA in December 2020.

There are current applications being assessed by the EMA, Health Canada, Switzerland, and Singapore.

**Coronaviruses:**

CoVs are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors . SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it recognizes the ACE2 receptor as the entry receptor. SARS-CoV-2 shares more than 79% of its sequence with the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B *Betacoronavirus*), and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV, a lineage C *Betacoronavirus*) (Lu et al 2020).

## Manufacturing and quality control (Module 3) data evaluation

[redacted]

**Quality – related proposed conditions of registration**

No be decided closer to the time of the final decision pending the data that has been received.

## Non-clinical (Module 4) data evaluation

There were no non-clinical objections to the provisional registration of the vaccine.

Summary of the report:

The sponsor has generally conducted adequate pharmacology studies. As part of a rolling submission limited toxicity studies were provided with AZD1222. A bio-distribution study and a main developmental and reproductive toxicity (DART) study in mice are pending.

Pharmacology:

Covid-19 Astra Zeneca was found to be immunogenic in BALB/c, CD-1 mice; ferrets; non human primates and pigs. Mice and pigs showed Th1 like CD4+ and CD8+ T cell responses. Pigs and inbred mice showed a response to booster vaccine. The lack of response in outbred mice was attributed to a higher initial dose. When vaccinated rhesus monkeys were exposed to COVID - 19, the clinical disease severity scores in the lungs were reduced, however there was no reduction in viral shedding from the nose. There was no evidence of VAED in vaccinated monkeys exposed to COVID-19. The pharmacology studies were designed to assess short term immunogenicity only.

Pharmacokinetics:

Three different mouse studies using three different ChAdOx1 vectors examined the biodistribution. Two of these showed no evidence of the adenovirus vector beyond the site of administration. The third show low levels of the ChAdOx1 vector were found in the heart, liver, ovary, testes and lymph nodes.

Toxicology

A repeat dose toxicology study was performed in mice. The vaccine (total viral particle dose 3.7 X $10^{10}$ ) was given over 6 weeks with a 4 week recovery period. Scheduled necroscopies were performed at the end of the 6 week treatment period or 28 day recovery period. Injections were associated with increased temperature, decreased monocyte count, increased globulin and decreased albumin/globulin consistent with an acute phase response. Higher spleen weights were observed.

Another study was performed to investigate the potential toxicity of ChAdOx1 Chik or ChAdOx1 MERS in inbred (Balb/c) mice aged 8 weeks old and weighing 20grams. The doses given were 1 X $10^{10}$ viral particles, in 25 or 35µL per injection. Vaccines were well tolerated with no adverse effects. Similarly a further 2 studies of mice with other vaccines containing the ChAdOx1 vector did not show any toxicity.

No genotoxicity or carcinogenicity studies are performed.

The ChADOx1 vector is expected to have negligible risks of integrating into the human genome or recombination with human adenovirus.

Reproductive and developmental toxicity

A study was performed in outbred CD-1 female mice either before mating and during gestation; or during the littering phase. The dose given was 2.59 X $10^{10}$ viral particles per dose, which is estimated to be approximately 906.5 fold the human dose. Dams produced and anti-S glycoprotein immune response. The foetuses and pups were seropositive, indicative of placental and lactational anti-S glycoprotein activity. There were no abnormal effects on female reproduction, fetal or pup survival and no abnormal gross pathology findings in pups or dams in either phase.

A mouse study of embryofetal development is ongoing.

## Clinical (Module 5) data evaluation

Please refer to the clinical evaluation report for more details

***Pharmacodynamics (PD)***

Vaccination with COVID-19 Astra Zeneca induces a cellular and humoral immune response.

There is no established immunological correlate of protection against SARS-CoV-2. The neutralizing antibody against the spike protein of SARS-CoV-2 is likely to be the best surrogate marker of efficacy. In seropositive patients, antibodies to RBD, anti-S antibodies and neutralising antibodies after a single standard dose were similar to that seen in convalescent plasma. These peaked at day 28 then remained stable. In seronegative patients, there was a further increase in antibodies after a second dose. Seropositive patients also had an antibody response to the vaccine. The s-specific antibodies are biased towards IgG1 and IgG3.

Cell mediated immunity was assessed by IFNλ ELISpot and pan ICS assay. IFNλ peaked at day 14 and remained stable, with no further increase after a second dose.

Anti-vector antibodies increased after the initial vaccination with no further increase after the second dose. Limited data was available as to how these affect antibodies to S protein.

## Efficacy

The clinical development program for AZD1222 consists of 9 clinical studies, 4 of these were used in the interim analysis.

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

| Study Identifiers<br>Region | COV001<br>(NCT04324606)<br>UK | COV002<br>(NCT04400838)<br>UK | COV003<br>(ISRCTN89951424)<br>Brazil | COV005<br>NCT04444674<br>South Africa |
|---|---|---|---|---|
| Sponsor | University of Oxford | University of Oxford | University of Oxford | University of Oxford |
| Start Date / Status | April 2020 / Ongoing | May 2020 / Ongoing | June 2020 / Ongoing | June 2020 / Ongoing |
| Phase | I/II | II/III | II/III | I/II |
| Design | Participant blind, randomised, controlled | Participant blind, randomised, controlled | Participant blind, randomised, controlled | Double blind, randomised, controlled |
| Planned number of participants | ~ 1077 | ~12390 | ~10300 | ~2070 |
| Characteristics of participants included in the pooled analyses | 18-55 yr, healthy | ≥ 18 yr, healthy | ≥ 18 yr, healthy | ≥ 18-65 yr, healthy |
| Number of doses (IM route) | 1 or 2<br>(based on study group) | 1 or 2<br>(based on study group) | 2 | 2 |
| AZD1222<br>dose levels [a] | SD: $5 \times 10^{10}$ vp<br>LD: $2.5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp<br>LD: $2.2 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp<br>LD: $2.2 \times 10^{10}$ vp[b] |
| Control | MenACWY | MenACWY | MenACWY (first dose)<br>Saline Placebo (second dose) | Saline Placebo |
| Planned Dose interval | 4 – 8 wk | 4 – 6 wk | 4- 12 wk | 4 wk |
| Case Detection | Passive | Passive and active (weekly swabbing, SARS-CoV-2 PCR) | Passive | Passive and active (by-visit nasal swabs and/or saliva collection, SARS CoV-2 PCR) |
| Planned duration of Follow-up | 364 days after the last dose | 364 days after the last dose | 364 days after the last dose | 364 days after the first dose |

All clinical trials have had number of protocol changes since commencement- COV001 has had 12, COV002 has had 14, COV003 has had 8 and COV005 has had 4.

Only studies CV002 and CV003 were used in the interim analysis for efficacy based on the date lock from 4th November 2020. This is because there were less than 5 cases detected in studies COV001 and COV005.

The dosing regimens (ie, number of doses, dose level, and dose schedule) chosen for the 4 University of Oxford-sponsored efficacy studies were selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts and other similar adenovirus vectored vaccines. Across the 4 ongoing studies, a single dose and a two-dose regimen were being evaluated. Two AZD1222 dose levels were a standard dose (SD) of approximately $5 \times 10^{10}$ vp and a low dose (LD) of 2.2 -2.5 $\times 10^{10}$ vp. Due to differences in concentration determination between analytical methods, a subset of participants in Studies COV002 and COV005 who were due to receive SD actually received LD.

The initial intent of this programme was to implement a one dose only immunization schedule. Following review of immunogenicity data from Study COV001, it became apparent that a second dose provided increased immunogenicity. This led to a decision to more extensively evaluate a two-dose schedule. In the context of logistical constraints related to the rapid conditions in which this clinical programme and scale-up manufacturing were initiated in parallel, delays occurred in clinical trial material availability for second dose vaccinations ,mainly the UK studies COV001 and COV002. The interval between doses 1 and 2 was originally intended to range from 4 to 12 weeks, however extended to as long as 26 weeks

*Efficacy Endpoint:*
The primary efficacy endpoint was patients with symptoms (either fever > 37.8 degrees, cough, shortness of breath, anosmia or ageusia) and a positive RT-PCR test for COVID-19.

**Table 5 Definitions of COVID-19 Cases for Evaluation of Efficacy**

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

[a] Virologically confirmed from RT-PCR or other nucleic acid amplification test.
[b] WHO clinical progression scale, presented in Table 4.

Secondary analysis included severe disease, death, asymptomatic cases, and subgroup analysis. Asymptomatic cases were only identified from study COV002 as this was the only study which included weekly PCR swabs for COVID-19.

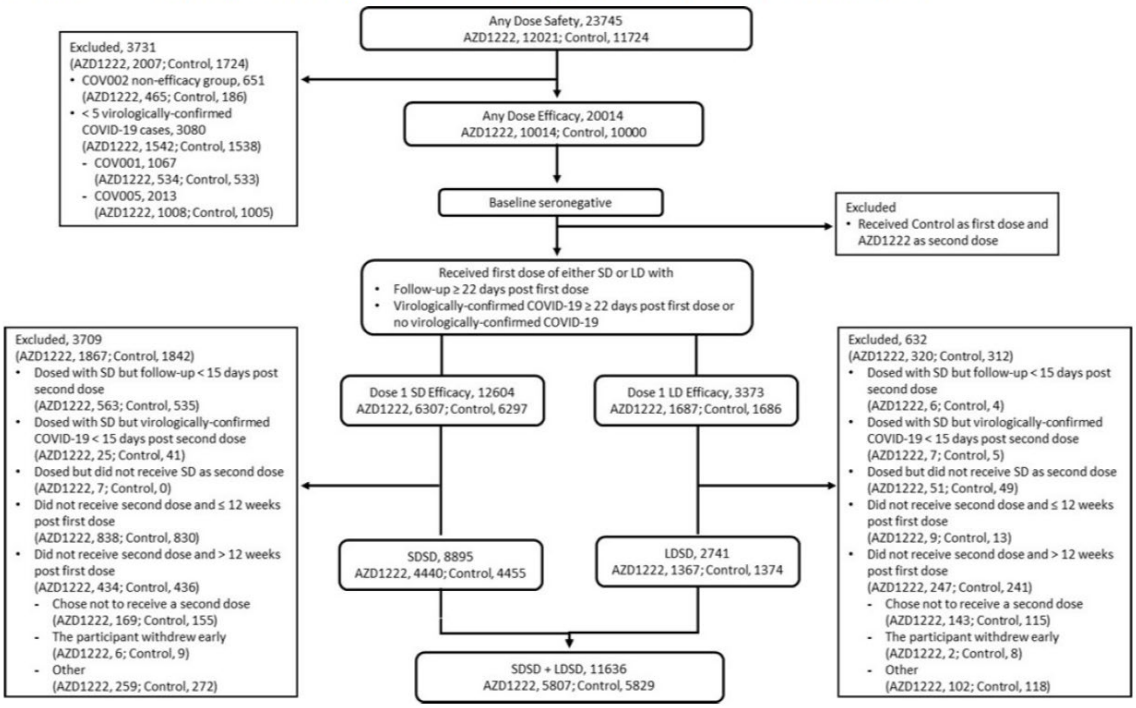
*Statistical methods:*

The interim pooled analysis was to occur when at least 53 cases of SARS-CoV-2 virologically confirmed symptomatic COVID-19 that occurred ≥ 15 days post the second dose had been reported in participants who received SDSD across the AZD1222 and control groups in pooled studies. This was expected to provide approximately 80% power for a 20% threshold for an assumed vaccine efficacy of 70% for the primary population (participants who received SDSD and LDSD). Due to the sudden rise in baseline incidence and rapid accumulation of cases prior to data cut-off, 131 events were included in the analysis, of which 98 were in participants that received the SDSD regimen.

A Poisson regression model with robust variance was used as the primary efficacy analysis model to estimate the relative risk on the incidence of SARS-CoV-2 virologically confirmed primary symptomatic COVID-19 between the AZD1222 and control groups. The model contained the terms of study code, treatment, age group at screening (18 to 55, 56 to 69, and ≥70 years). The logarithm of the period at risk for the primary endpoint for primary analysis was used as an offset variable in the model to adjust for participants having different follow up times during which the events occurred. Vaccine efficacy (VE), which was the incidence in the vaccine group relative to the incidence in the control group expressed as a percentage, was calculated as VE = 1- relative risk. The VE, and its corresponding 2-sided (1-α)% CI, were estimated from the model.

*Participant disposition:*
As of the data cut off point 4th November 2020, 23745 participants had been randomised to one of the 4 studies, received at least one dose of study intervention and met the inclusion criteria for inclusion in the pooled analysis. Almost all (99.4%) of these participants are ongoing. The full efficacy population includes 20014 participants, 10014 who had received AZD 1222 and 10000 who received control. Approximately half of the participants were included in the primary efficacy analysis population, the most common reason for exclusion was not having received 2 doses of vaccine.

**Figure 3** **Disposition of Participants for the Efficacy Analysis Sets (AZD1222 Pooled Analysis)**




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

Source: Main Safety Tables 1.1.1.1 and 1.1.2.1; Supplemental Tables IEMT55.1 and IEMT55.2, Module 5.3.5.3 (previously submitted 24 Dec 2020)

*Demographics:*

In the primary efficacy population, the mean age of participants was 41.52 years. There were in total 660 participants (5.7%) over 65 years and 444 (3.8% ) over 70 years. Approximately 60% of participants were female. In relation to race, 83.4% were white, 4.4% were Asian, 4.1% were Black. There were 20.2% with a BMI of > 30kg/m$^2$. All participants were seronegative (to nucleic acid) at baseline.

**Table 9** **Demographics and Baseline Characteristics**

| Characteristic | Statistics | SDSD + LDSD Seronegative for Efficacy Analysis Set | | |
|---|---|---|---|---|
| | | AZD1222 (N=5807) | Control (N=5829) | Total (N=11636) |
| Age (years) at screening | n | 5807 | 5829 | 11636 |
| | Mean | 41.56 | 41.48 | 41.52 |
| | SD | 12.72 | 12.65 | 12.68 |
| | Median | 40.00 | 40.00 | 40.00 |
| | Min | 18.0 | 18.0 | 18.0 |
| | Max | 86.0 | 88.0 | 88.0 |
| Age group, 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) |

*Efficacy*

The median duration of follow up since the first dose was 132 days (4 months). The median duration of follow up 15 days after the second dose was 48 days. The duration of follow up 15

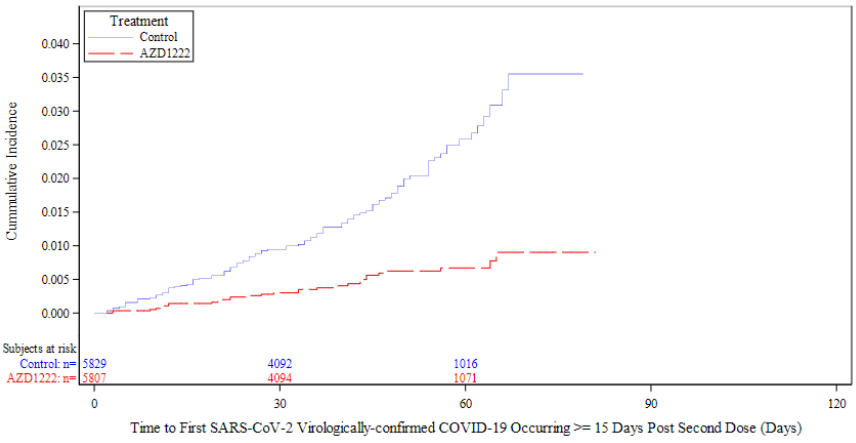
days after the second dose was longer after the LDSD group (59 days) than the SDSD group (39 days).

Primary Efficacy Endpoint:
The interim analysis was planned using the number of cases in the SDSD seronegative group. The sponsor proposed that the combined LDSD and SDSD seronegative population should be used for the primary efficacy population due to the greater power of the numbers, and presumed similar efficacy in the LDSD population based on immunology. Depending on which population is used, the vaccine efficacy is 60-70% with a lower 95% confidence interval of over 40%. This meets the EMA and FDA criteria for efficacy of a COVID vaccine that states the point estimate should be over 50% with lower 95% confidence interval over 30%.

**Table 12** **Primary Endpoint - Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose**

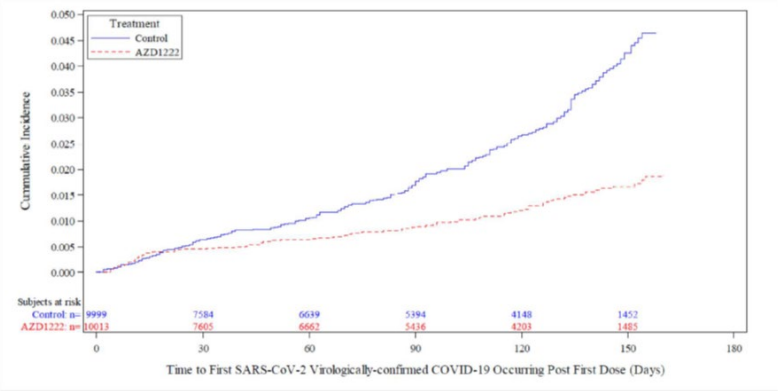
| | Participants with events | | | | | |
|---|---|---|---|---|---|---|
| | AZD1222 | | Control | | VE | 95.84% CI |
| Analysis population | N | n (%) | N | n (%) | (%) | (%) |
| **Primary endpoint:** SDSD + LDSD, seronegative | 5807 | 30 (0.52) | 5829 | 101 (1.73) | 70.42 | (54.84, 80.63) |
| SDSD + LDSD ITT, seronegative | 5814 | 31 (0.53) | 5831 | 100 (1.71) | 69.13 | (53.10, 79.68) |
| SDSD, seronegative | 4440 | 27 (0.61) | 4455 | 71 (1.59) | 62.10 | (39.96, 76.08) |

The figure below is the Kaplain Meir curve (actually a survival curve) for primary efficacy in the combined LDSD and SDSD seronegative population. It is important to note the rapidly decreasing denominator over time. There is survivor bias in this analysis, in that patients who contract COVID are excluded. There is also the bias introduced by duration of follow up, in that the longer the duration of follow up the greater the exposure and the more likely an event is likely to occur.




In the full efficacy population (Any dose for Efficacy Analysis set), who received at least one dose with follow up from the first dose. Efficacy of the AZD1222 vaccine was 52.69% (95% CI: 40.52%, 62.37%) against COVID-19 in this group of participants. The vaccine appears to be effective from around 21 days after the first dose.

**Figure 8** **Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus)**




There were very few patients with severe disease and hospitalisation in the interim analysis. In the SDSD population, there were 0/4440 participants who received AZD1222 hospitalised, and 4/4455 in the control group. One patient required ICU and died in the control group.

Asymptomatic COVID-19 was assessed in Study COV002. Code-bar tagged swabs were distributed to participants to support weekly traceable results of self-swabbing for detection of SARS-CoV-2 infection. Swabs were sent for RT-PCR testing at National Health Service (NHS) laboratories. Participants were also asked to self-record whether they experienced symptoms or not. Participants who had a virologically confirmed SARS-CoV-2 infection and reported that they had no symptoms are referred to here as 'asymptomatic'; those participants who did not report whether they had symptoms or not are referred to here as 'unknown'.

There were similar, or numerically lower, number of asymptomatic or unknown cases in the LDLD+ SDSD groups, importantly not an increase number of cases like you may expect if there were less symptomatic cases.

**Table 16** **Vaccine Efficacy for Incidence of Asymptomatic SARS-CoV-2 Infection Occ Dose (for Study COV002 only)**

| | | Participants with events, n (%) | | | |
|---|---|---|---|---|---|
| **Analysis population** | **COVID-19 case definition** | **N** | **AZD1222** | **N** | **Control** |
| SDSD + LDSD for COV002, seronegative | Asymptomatic SARS-CoV-2 infection | 3744 | 11 (0.29) | 3804 | 20 (0.53) |
| | Asymptomatic or unknown symptoms SARS-CoV-2 infection | 3744 | 29 (0.77) | 3804 | 40 (1.05) |
| SDSD for COV002, seronegative | Asymptomatic SARS-CoV-2 infection | 2377 | 8 (0.34) | 2430 | 11 (0.45) |
| | Asymptomatic or unknown symptoms SARS-CoV-2 infection | 2377 | 22 (0.93) | 2430 | 23 (0.95) |

**Efficacy in subpopulations:**
Co-morbidity:
Although 36% of the patient population had co-morbidities, most of these were mild (see CER section 13.3.1). The mean age of those with comorbidities was greater and a greater proportion were over 65 years (8.4% versus 4.15). Also, the duration of follow up was shorter in the AZD1222 group (38 days) than the control group (47 days). In the combined LSSD and SDSD seronegative population, 11/2070 in the AZD 1222 group and 43/2133 in the control group met the primary efficacy endpoint.

Age
As previously mentions, only 660 adults were included in the primary efficacy population. There were insufficient data to assess efficacy.

Efficacy was similar in the UK and Brazil.

**Dose and Dose Interval**
The greater efficacy in the LDSD data set is noted. Although this is interesting, this will not be pursued from a regulatory viewpoint due to the multitude of confounding factors (longer duration of follow up, longer dose interval, only UK data set, younger participants).

Efficacy after a single dose was described earlier in the efficacy analysis and is in the order of 60%. A subsequent analysis of the efficacy of a single dose was performed using those who received either SD or LD as the first dose, and were follow from 22 days after the first dose to 12 week after the first dose. In this population there were 12/7998 symptomatic cases in the AZD 1222 group and 44/7982 in the control group, VE 73%, 95% CI 48.8 to 85.8).

The sponsor performed analysis of efficacy by dose interval and identified a trend for greater efficacy with increasing dose interval. However, there are some inconsistencies in this data.

**Table 28** **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)**

| | Participants with events, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose interval | N | AZD1222 n (%) | N | Control n (%) | VE (%) | 95% CI (%) | P-value |
| < 6 weeks | 1702 | 9 (0.53) | 1698 | 19 (1.12) | 53.28 | (-3.21, 78.86) | 0.060 |
| 6–8 weeks | 562 | 5 (0.88) | 521 | 9 (1.73) | 51.08 | (-45.57, 83.56) | 0.199 |
| 9–11 weeks | 1056 | 9 (0.85) | 1110 | 24 (2.16) | 60.55 | (15.23, 81.64) | 0.017 |
| ≥ 12 weeks | 1120 | 4 (0.36) | 1126 | 19 (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 from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.
The observation period for the endpoint was 15 days post second dose up to 1 year in study.
COVID-19 endpoints were based on adjudicated events.

The increasing efficacy with increasing dose interval is supported by the immunology data which demonstrated increased antibody responses with greater dose intervals.

**Table 27** **Quantification of nAbs (by Pseudoneutralisation Assay) Levels for Different Regimens (Dose Level and Interval) (Seronegative at Baseline)**

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

Sources: Supplemental Tables IEMT 46.1.4.2.a, IEMT 46.1.4.2.b, IEMT 46.1.4.2.c IEMT 46.1.4.2.d, IEMT 46.1.4.3.a, IEMT 46.1.4.3.c, and IEMT 46.1.4.3.d, Module 5.3.5.3 (previously submitted 24 Dec 2020)

## Safety

*Experience with other ChAdOx1 vaccines:*
Over 240 healthy adult volunteers have received ChAdOx1-vectored vaccines in previous clinical studies sponsored by the University of Oxford with immunogens from multiple pathogens such as influenza, chikungunya, tuberculosis, and MERS as well as prostate cancer. In addition, the ChAdOx1 platform has been developed with immunogens from malaria, meningitis B, Zika, and hepatitis B, with clinical studies ongoing in healthy volunteers, and with an immunogen from HIV to act as a therapeutic vaccine, with 2 studies in HIV patients currently being performed. The vaccines are not associated with safety concerns other than anticipated reactogenicity events.

*Meta-analysis*
Safety was assessed in all studies by evaluation of solicited AEs commonly associated with vaccinations, unsolicited AEs, SAEs (including deaths) and AESIs. Biochemistry and haematology clinical laboratory tests were also evaluated for a subset of participants in studies COV001, COV002, and COV005.

There were 2375 participants in the any dose for safety analysis set. The median number of days follow up after the first dose was 105 in the AZD 1222 group and 104 in the control group. Approximately 2/3 of participants received 2 doses, and 1/3 of participants received 1 dose. In the safety data set, 8.7% were over 65 years (1169 exposed to AZD 1222) and 6.8 % were over 70 years (821 exposed to AZD 1222). The safety population included around 20% of the population with a BMI > 30kg/m$^2$, 2.5% with diabetes, 6.1% had hypertension.

SOLICITED
Solicited local and systemic adverse events occurred in most participants, but were generally mild and short lived.

**Table 9** **Overall Summary of Solicited Adverse Events Collected Within 7 Days After Vaccination: Pooled Analysis (Dose 1 SD for Safety Analysis Set)**

| | Days 0 to 7 After Any Vaccination | | Days 0 to 7 After First Vaccination | | Days 0 to 7 After Second Vaccination | |
|---|---|---|---|---|---|---|
| | AZD1222 (N = 10069) | Control (N = 9902) | AZD1222 (N = 10069) | Control (N = 9902) | AZD1222 (N = 10069) | Control (N = 9902) |
| Evaluated for solicited AEs, n | 2 648 | 2 497 | 2580 | 2425 | 1662 | 1526 |
| Any solicited AE, n (%) | 2277 (86.0) | 1791 (71.7) | 2161 (83.8) | 1637 (67.5) | 1026 (61.7) | 722 (47.3) |
| Any solicited local AE, n (%) | 1979 (74.7) | 1258 (50.4) | 1839 (71.3) | 1117 (46.1) | 778 (46.8) | 456 (29.9) |
| Any ≥ Grade 3 severity solicited local AE, n (%) | 252 (9.5) | 138 (5.5) | 210 (8.1) | 112 (4.6) | 70 (4.2) | 38 (2.5) |
| Any solicited systemic AE, n (%) | 1932 (73.0) | 1488 (59.6) | 1817 (70.4) | 1320 (54.4) | 741 (44.6) | 545 (35.7) |
| Any ≥ Grade 3 severity solicited systemic AE, n (%) | 221 (8.3) | 63 (2.5) | 192 (7.4) | 41 (1.7) | 37 (2.2) | 27 (1.8) |

In the Dose 1 SD for Safety Analysis Set, the most frequently reported solicited local injection site AEs within 7 days after either vaccination with AZD1222 were tenderness (63.7% vs 39.5% in control) and pain (54.2% vs 36.7% in control). Other solicited local injection site AEs reported in ≥ 10% of AZD1222 participants were warmth (17.7% vs 14.5% in control), redness (14.0% vs 8.8% in control), itch (12.7% vs 7.5% in control), and swelling (10.0% vs 5.8% in control). Solicited local AEs with ≥ Grade 3 severity after any vaccination of AZD1222 reported in ≥ 2% of participants included swelling (5.3%), redness (4.8%), and induration (4.1%). No Grade 4 events were reported.

In the Dose 1 SD for Safety Analysis Set, the most frequently reported solicited systemic AEs within 7 days after either vaccination with AZD1222 were fatigue (53.1% vs 38.2% in control) and headache (52.6% vs 39.0% in control); other frequently reported systemic solicited AEs were muscle pain (44.0% vs 21.6% in control), malaise (44.2% vs 20.2% in control), feverishness, (33.6% vs 10.7% in control), chills (31.9% vs 8.3% in control), joint pain (26.4% vs 12.4% in control) nausea (21.9% vs 13.1% in control), and fever (7.9% vs 1.2% in control). Solicited systemic AEs with ≥ Grade 3 severity after any vaccination with AZD1222 reported in ≥ 2% of participants included malaise (3.8%), feverishness (3.5%), chills (3.5%), fatigue (3.2%), and headache (2.7%). A single Grade 4 event was reported in the AZD1222 group for fever.

Solicited AEs were less common after the second dose, and less common in the elderly.

UNSOLICITED
In the Any Dose for Safety Analysis Set, 37.8% of participants in the AZD1222 group and 27.9% of participants in the control group reported an unsolicited AE within 28 days following any vaccination. Unsolicited AEs were less common after the second vaccine.

Serious AEs were reported in 0.7% of participants in the AZD1222 group and 0.8% of participants in the control group. Very few, < 0.1% in each treatment group, were considered related to the investigated product. A total of 6 SAEs with a fatal outcome (2 in the AZD1222 group and 4 in the control group) occurred as of the cut-off date. None of these were thought to be due to the vaccine. AESIs occurred in 0.8% of participants in the AZD1222 group and 1.1% of participants in the control group.

All of the unsolicited AEs were typical of those reported for vaccines.

**Table 16** **Unsolicited Adverse Events within 28 Days Following Vaccination (≥ 2% in Either Treatment Group) by PT: Pooled Analysis (Dose 1 SD for Safety Analysis Set)**

| | Number (%) of Participants [a] | |
|---|---|---|
| PT (MedDRA version 23.1) | AZD1222 (N = 10069) | Control (N = 9902) |
| Vaccination site pain | 1197 (11.9) | 733 (7.4) |
| Headache | 1051 (10.4) | 685 (6.9) |
| Pyrexia | 852 (8.5) | 210 (2.1) |
| Myalgia | 852 (8.5) | 345 (3.5) |
| Fatigue | 487 (4.8) | 290 (2.9) |
| Chills | 392 (3.9) | 100 (1.0) |
| Asthenia | 262 (2.6) | 123 (1.2) |
| Malaise | 243 (2.4) | 138 (1.4) |
| Nausea | 211 (2.1) | 117 (1.2) |

SAE
In the AZD1222 group, there was one case of MS and one case of transverse myelitis, both unlikely to be related to investigational agent.
In the control group there was one case of myelitis and one case or haemolytic anaemia.

USE IN PREGNANCY
Women who were pregnant, lactating, or intended to become pregnant were excluded from the university of Oxford studies, and women of childbearing capacity were required to use continuous birth control.

As of the data cut off of 4 November 2020, there were 17 pregnancies reported in the AZD 1222 pooled analysis set, 10 participants in the AZD 1222 group and 7 in the control group. In the AZD 1222 group, there was 1 termination of pregnancy and 1 spontaneous miscarriage. In the control group, there were 2 reports of termination of pregnancy and 2 spontaneous miscarriage. In addition to the above cases, there were four cases of pregnancy in the COV005 global safety database. There was 1 spontaneous miscarriage in the AZD1222 group and 1 in the control group. No data on the outcome of the pregnancies is noted.

## Risk Management Plan (RMP) evaluation

AstraZeneca Pty Ltd has submitted EU-RMP Version 1.0 Succession 1.0 (date 21 December 2020; DLP 4 November 2020) and ASA Version 1.0 Succession 1.0 (date 22 December 2020) in support of this application. With the responses to rolling questions sent on 30 December 2020, the sponsor provided an updated ASA version 1.0 Succession 2 (date 13 January 2021)

The summary of safety concerns are outlined in the following table

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **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 | ✓ | ✓* | ✓ | – |

Pharmacovigilance activities include monthly summary safety report, there is one effectiveness study and 4 post authorisation safety studies. A pregnancy registry is planned to be conducted to estimate the frequency of selected adverse pregnancy outcomes in women receiving at least 1 dose of the vaccine during pregnancy or up to a predefined period before estimated date of conception.

| Study | Objectives | Safety Concerns addressed | Milestones |
|---|---|---|---|
| Enhanced Active Surveillance Study<br>A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222 (D8111R00003 / D8111R00004) | Primary Objectives:<br>To assess the safety and tolerability of at least 1 dose of the AZD1222 in adults ≥ 18 years of age for a predefined period (eg, 3 months) after vaccination with first dose of AZD1222.<br>Secondary Objectives:<br>To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 12 months after vaccination with first dose of AZD1222<br>Secondary Objectives (pregnancy sub-study):<br>To estimate the frequency of selected adverse pregnancy outcomes in women receiving the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception. | Immune-mediated neurological Conditions, Vaccine-associated enhanced disease, use in pregnant and breastfeeding women, subjects with severe immunodeficiency, subjects with severe and/or uncontrolled underlying disease and use with other vaccines | Study protocol available by 01 March 2021 |
| AZD1222 Pregnancy Registry:<br>Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy | To estimate the frequency of selected adverse pregnancy outcomes (ie, spontaneous abortions, stillbirths, and preterm births) in women receiving at least 1 dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg 60 days) before estimated date of conception.<br>To estimate the frequency of selected adverse foetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 6 months of life (to account for diagnosis of major congenital malformations that might be delayed) in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception. | use in pregnant and breastfeeding women | Study protocol available by 01 March 2021 |
| Post-marketing safety study:<br>A post-authorisation/ Post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns. | To estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222, among all populations targeted for vaccination and in the specific populations considered as missing information<br>To estimate the relative risk (comparing exposed and unexposed person time) of safety concerns including adverse events of interest among all populations targeted for vaccination and in the specific populations considered as missing information<br>To characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information. | Immune-mediated neurological Conditions, Vaccine-associated enhanced disease, use in pregnant and breastfeeding women, subjects with severe immunodeficiency, subjects with severe and/or uncontrolled underlying disease and use with other vaccines | Study protocol available by 01 April 2021 |
| Post-marketing effectiveness study:<br>Post-authorisation/ Post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public private partnership with COVIDRIVE utilising primary data collected prospectively through the COVIDRIVE platform. (D8111R00005) | To estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 in hospitalized patients, overall and by age group (< 18, 18-64 and ≥ 65 years old), after adjusting for potential confounders. | N/A | Study protocol expected March 2021 (COVIDRIVE consortium) |

In addition to these measures proposed by the sponsor, the TGA's signal investigation unit has strengthened the process for monitoring and responding to all safety related issues associated with COVID-19 vaccines in the post market setting. Enhanced active

surveillance will be conducted by AusVaxSafety and will enable rapid identification of adverse events and also early identification of potential quality issues. Sponsor's of COVID-19 vaccines are expected to conduct batch specific pharmacovigilance measures to ensure timely detection and handling of both batch specific safety signals and batch specific reports or reduced effectiveness or vaccine failure. The COVID-19 taskforce of the Department of Health will implement traceability process at a national level.

Only routine risk minimisation measures are proposed. The PI and the CMI together with the information/training expected to be provided by the Department of Health/ COVID-19 Vaccine Taskforce are anticipated to adequately mitigate the risks associated with this vaccine. If the current understanding of the safety profile of this vaccine changes, the risk minimisation plan will require to be re-assessed.

The evaluator has recommended the sponsor include

- 'safety in the elderly' as missing information in the summary of safety concerns
- 'long term safety' as missing information in the summary of safety cxoncerns
- The following events in the list of AESI : acute cardiac injury including microangiopathy, heart failure and cardiogenic shock, stress cardiomyopathy, coronary artery disease and arrhythmia, anosmia, ageusia, chilblain like lesions, erythema multiforme.

**RMP evaluator recommendations regarding condition/s of registration:**

To be confirmed after the results of the CHMP decision and update to the EU-RMP, as well as after the ACV discussion

## Clinical Study Plan for Provisional Registration.

As part of the provisional registration process, sponsor's are required to submit a clinical study plan whereby they demonstrate how any limitations present at the time of interim analysis will be addressed.

The sponsor's provisional approval clinical study plan included submitting the full study reports of COV001, COV002, COV003 and COV004 by March 2022. In addition, the sponsor planned to submit the interim analysis from the ongoing US/Chile/Peru study D8110C00001 by March 2021.

*Delegate's comments on the clinical study plan:*

This clinical study plan will assist in providing further information in relation to long term efficacy, long term safety, and use in the elderly. It should also include further information about use in immunosuppressed individuals (including patients with HIV).

Although not officially part of the clinical study plan, the ongoing post market surveillance, pregnancy register, and post authorisation safety studies will help inform use in pregnancy and in patients with other co-morbidities. It is recommended that the ongoing studies also form part of the clinical study plan.

The sponsor should also provide the TGA with the studies evaluating co-administration of influenza (and any other vaccines).

The main gap in the proposed ongoing studies is in relation to the optimal dose and dosing interval for vaccine efficacy. The sponsor is requested to provide further information about and proposed future studies.

### Other Ongoing studies:

**Table 2 Additional Studies in the Clinical Programme[a]**

| Study Identifiers Region | COV004 (PACTR20200568189 5696) Kenya | D8110C00001 (NCT04516746 EudraCT number 2020-001228-32) United States, Chile, Peru | D8111C00001 Russia | D8111C00002 (NCT04568031) Japan | ICMR/SII-COVISHIELD India |
|---|---|---|---|---|---|
| Sponsor | University of Oxford | AstraZeneca | AstraZeneca | AstraZeneca | ICMR/SIIPL |
| Start Date/Status | October 2020 / Ongoing | August 2020 / Ongoing | On Hold[b] | August 2020 / Ongoing | August 2020 / Ongoing |
| Phase | Ib/II | III | III | I/II | II/III |
| Design | participant-blind, randomised, controlled | double-blind, randomised, controlled | Open label | double-blind, randomised, controlled | observer-blind, randomised, controlled |
| Planned number of participants | ~400 | ~30000 | ~100 | ~256 | ~1600 |
| Participant characteristics | ≥ 18 yr, healthy | ≥ 18 yr, healthy or with medically-stable chronic disease | ≥ 18 yr, healthy | ≥ 18 yr, healthy | ≥ 18 yr, healthy |
| Number of doses (IM route) | 1 | 2 | 1 | 2 | 2 |
| AZD1222 dose levels [c] | SD: $5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp | SD: $5 \times 10^{10}$ vp OR COVISHIELD: $5 \times 10^{10}$ vp |
| Control | Rabies vaccine | Saline Placebo | None | Saline Placebo | Placebo (Vaccine vehicle) |
| Planned dose interval | - | 4 wk | - | 4 wk | 4 wk |
| Case detection | Passive | Passive and active (weekly contacts) | Not applicable | Passive | Passive |
| Planned duration of Follow-up | ~365 days after the dose | ~730 days after the first dose | ~180 days after the dose | ~365 days after the first dose | ~180 days after the last dose |

## Discussion

The clinical development program for the AZD1222 occurred in the midst of a pandemic. There have been a number of changes to the protocols which make interpretation of the trials challenging.

The sponsor has reported the primary efficacy endpoint using a range of different populations. In all of these populations, the point estimate for vaccine efficacy was over 50% and lower 95% confidence over 30%, thus meeting the requirement for EMA and FDA in terms of an effective COVID vaccine. The vaccine efficacy was highest in the SDSD+LDSD seronegative analysis set, possibly bias due to younger patient population, longer duration of follow up and longer dose interval. It was lowest in the any dose efficacy data set, as this included both one and 2 doses and variable periods of follow up. I consider the SDSD population as most relevant for the regulatory decision.

The study was not powered for secondary analysis – thus firm conclusions cannot be drawn from this. However there appeared to be lower number of patients requiring hospitalisation. The COV002 study included active screening for asymptomatic COVID-19. Participants were required to perform and return their own swab. The results are uninterpretable due to low numbers and incomplete compliance. Animal studies have shown reduced viral load in the lower respiratory tract but persistent spreading in the upper respiratory tract. At this stage, efficacy in preventing asymptomatic disease and transmission is unknown.

Although the AZD1222 vaccine passes the statistical requirement for efficacy, the ACV are asked to comment upon whether the efficacy demonstrated is adequate to meet the objectives of the Australian Vaccination Strategy. It is important that the population understand the facts about the efficacy of the vaccine, and limitations of the data, and the need to continue other public

health measures to prevent the spread of disease until more information about vaccine efficacy is available.

One of the major limitations in the study is the short and variable duration of follow up. The duration of follow up, and reasons for missing data in follow up, are important in determining efficacy. Lower duration of follow up may be from drop outs, but may also arise due to sensoring of cases. Longer duration of follow up increases the time of exposure and increases the opportunity for true effectiveness (or non-effectiveness ) to be demonstrated.

Variable doses and variable dose intervals arose due to procedural issues in the study. Although the AZD1222 and control groups were equally affected, different subgroups within the meta-analysis were unequally affected. For regulatory purposes, the sponsor is proposing the standard dose of 5 X $10^{10}$ vp and a two dose regime, 4-12 weeks apart. This is supported by primary efficacy analysis. And will be confirmed by ongoing studies. The post hoc exploratory subgroup analysis suggested greater efficacy (and immunogenicity) with longer dose intervals, such that the best dose regimen may be 12 weeks between doses. This is supported by adequate protection of a single dose for up to 12 weeks, and adequate protection after 2 doses for after 12 weeks. The optimal dose interval within the 4-12 week interval for the vaccine roll out is best left to the immunisation task force for consideration.

Another limitation to the clinical development program was that those at high risk of COVID -19, including the elderly and those with significant co-morbidities, were excluded or under-represented. From a regulatory perspective, under the Therapeutic Goods Act the delegate must be satisfied that 'quality safety and efficacy have been adequately established for the purpose for which they are to be used'. This is a different assessment to a risk/benefit analysis as the potential risks of vaccination are small, and the potential benefits in this population large. In my opinion as delegate, these populations should not be excluded from the indication as it is reasonable to extrapolate efficacy, and the risks of COVID-19 outweigh potential risks of the vaccine. But there needs to be adequate warning about the limitations of the data in the PI, and a recommendation to prescribers that the potential risks and benefits to an individual be considered prior to proceeding to vaccinate.

Similar limitations apply to the data available for use in pregnancy. However, not only was there insufficient patients in the study but also incomplete pre-clinical studies. The proposed pregnancy category is B2. The ACV will be requested to advice on the adequacy of the warning for use in pregnancy.

## Conclusions

I am of the opinion that the ChAdOx1-nCoV-2 Astra Zeneca vaccine be approved for provisional registration. The ACV is requested to assist in the responses to a number of questions and in drafting the wording of some sections of the PI.

There are a number of outstanding studies that will be required to be submitted before full approval to address limitations in the data. It is important that the PI is kept up to date with this information.

There is a s14 exemption for the labelling to accommodate the supply of vaccines from Europe.

## References/attachments for ACM

| Number | Document name | Location/ID | ACM attachment |
|---|---|---|---|
| 1 | Quality evaluation reports | D20-3727121 | ☒ |
| 2 | Non clinical evaluation report | D20-3849280 | ☒ |
| 3 | Clinical evaluation report | D21-2111228 | ☒ |
| 4 | RMP evaluation report | D21-2055659 | ☒ |
| 5 | Statistics report | D21-2067875 | X |
| 6 | Sponsor's most recent PI | | |
| 7 | EMA considerations for COVID-19 vaccine approval (for reference) | D21-2113131 | X |
| 8 | Opinion regarding case of myelitis | D21-2104574 | X |
| 9 | WHO Design of Vaccine Efficacy trials to be used during Public Health Emergencies- Points of Considerations and Key Principals | https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-(4th-consultation)/ap1-guidelines-online-consultation.pdf | |

# Appendix 1: Review of the Product Information

## 1 NAME OF THE MEDICINE

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

## 3 PHARMACEUTICAL FORM

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

COVID-19 Vaccine AstraZeneca has provisional approval for the indication:

Active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

The use of this vaccine should be in accordance to official recommendations

The decision has been made on the basis of short term efficacy and safety data. Continues approval is dependent upon the evidence of longer term efficacy and safety from ongoing clinical trials and post market assessment.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks after the first dose. (see Section 5.1 Pharmacodynamic properties).

It is recommended that individuals who receive a first dose of COVID-19 Vaccine AstraZeneca complete the vaccination course with COVID-19 Vaccine AstraZeneca (see Section 4.4 Special warnings and precautions for use).

### 4.3 CONTRAINDICATIONS

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with any vaccine, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients. The vaccine should be used along with other infection control measures to prevent acquiring COVID-19.

Immunisation reduces the risk of symptomatic disease, but does not eliminate the risk of acquiring COVID-19. Individuals who test positive for COVID-19 on PCR swab may still be infectious and require isolation.

**Hypersensitivity**

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

**Concurrent illness**

As with other vaccines, administration of COVID-19 Vaccine AstraZeneca should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

**Thrombocytopenia and coagulation disorders**

As with other intramuscular injections, COVID-19 Vaccine AstraZeneca should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

**Neurological events**

Very rare events of demyelinating disorders have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine AstraZeneca should be considered.

**Immunocompromised individuals**

It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.

**Duration and level of protection**

The duration of protection has not yet been established.

**Interchangeability**

There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines.

**Use in the elderly**

There is currently limited data available for the efficacy and safety in individuals over 65 years of age and those with significant co-morbidities. The decision to immunise an individual should be made on the basis of potential benefits over risks to that individual.

**Paediatric use**

The safety and efficacy of COVID-19 Vaccine AstraZeneca in children and adolescents (aged <18 years old) have not yet been established. No data are available.

**Effects on laboratory tests**

Vaccination AZ-COVID 19 will lead to the development of antibodies to protein S and RBD. Vaccination does not interfere with the results of PCR testing. Patients with PCR swab should be treated as infectious.

### 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### 4.6 FERTILITY, PREGNANCY AND LACTATION

It is unknown whether COVID-19 Vaccine AstraZeneca may impact fertility. No data are available.

**Use in pregnancy – Category B2**

There are a limited amount of data from the use of COVID-19 Vaccine AstraZeneca in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine associated risk.

Animal reproductive toxicity studies have not been completed.

As a precautionary measure, vaccination with COVID-19 Vaccine AstraZeneca is not recommended during pregnancy. Use of COVID-19 Vaccine AstraZeneca in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

**Use in lactation**

There are no or limited data from the use of COVID-19 Vaccine AstraZeneca in lactating women. A risk to breastfed newborns/infants cannot be excluded.

As a precautionary measure, it is preferable to avoid vaccination with COVID-19 Vaccine AstraZeneca when breastfeeding.

### 4.7 AFFECTS ON ABILITY TO DRIVE AND USE MACHINES

### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### 4.9 OVERDOSE

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-COV-2. Following administration, the S glycoprotein of SARS-COV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

## Clinical trials

This section will be updated as evidence emerges from ongoing clinical studies.

### Interim analysis of pooled data from COV001, COV002, COV003, and COV005

COVID-19 Vaccine AstraZeneca has been evaluated based on an interim analysis (data lock 4th November 2020) of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001

(NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (NCT04400838), in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005 (NCT04444674), in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression. All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

Based on the pre-defined criteria for interim efficacy analysis, COV002 and COV003 exceeded the threshold of ≥5 virologically confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis; COV001 and COV005 were excluded.

In the pooled analysis for efficacy (COV002 and COV003), participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Participants randomised to COVID-19 Vaccine AstraZeneca received either two standard doses [SD] ($5\times10^{10}$ vp per dose) or one low dose [LD] ($2.2\times10^{10}$ vp) followed by one SD ($5\times10^{10}$vp), administered via IM injection.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks. The data available for the LDSD regime suggested promising results, however as this was a small subgroup and there were multiple possible confounding factors that may have affected the results, this regime was not considered appropriate for regulatory approval.

Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. In the pooled analysis, 94.1% of participants were 18 to 65 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing mild comorbidity (defined as a BMI ≥30 Kg/$m^2$, cardiovascular disorder, respiratory disease or diabetes). At the time of interim analysis the median follow up time post-dose 1 was 4.7 months and post dose 2 2.2 months

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of

131 participants had SARS-COV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-COV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2).

**Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]**

| Population | COVID-19 Vaccine AstraZeneca | | Control | | Vaccine efficacy % (95.84% CI) |
|---|---|---|---|---|---|
| | N | Number of COVID-19 | N | Number of COVID-19 | |

| | | cases[b], n (%) | | cases[b], n (%) | |
|---|---|---|---|---|---|
| ***Primary analysis population*** | | | | | |
| Overall (SDSD + LDSD) | 5807 | 30 (0.52) | 5829 | 101 (1.73) | 70.42 (58.84, 80.63) |
| ***Licensing regimen*** | | | | | |
| SDSD | 4440 | 27 (0.61) | 4455 | 71 (1.59) | 62.10 (39.96, 76.08) |

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low dose; SD = Standard dose [a] Primary study endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses (SDSD or LDSD) and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee

Consider adding other secondary/supportive endpoints:
- Efficacy of a single dose

Other secondary/exploratory endpoints are of clinical interest, however may not be robust due to the heterogeneity and confounding and biases in the study. In addition the short term follow up and lack of power have the potential to make the results unreliable and likely to cause confusion to the wider public.

**Immunogenicity**

**Interim analysis of pooled data from COV001, COV002, COV003, and COV005**

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against COVID-19 is unknown.

Following vaccination with COVID-19 Vaccine AstraZeneca, in participants who were seronegative at baseline, seroconversion (as measured by a ≥4 fold increase from baseline in S-binding antibodies) was demonstrated in ≥98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (see Table 3).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies.

**Table 3 SARS-COV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca (SDSD)[a]**

| Population | Baseline | 28 days after dose 1 | 28 days after dose 2 |
|---|---|---|---|
| | GMT (95% CI) | GMT (95% CI) | GMT (95% CI) |

| | | | |
|---|---|---|---|
| Overall | (N=882)<br>57.18<br>(52.8, 62.0) | (N=817)<br>8386.46<br>(7758.6, 9065.1) | (N=819)<br>29034.74<br>(27118.2, 31086.7) |
| ***Dose Interval*** | | | |
| <6 weeks | (N=481)<br>60.51<br>(54.1, 67.7) | (N=479)<br>8734.08<br>(7883.1, 9676.9) | (N=443)<br>22222.73<br>(20360.50, 24255.3) |
| 6-8 weeks | (N=137)<br>58.02<br>(46.3, 72.6) | (N=99)<br>7295.54<br>(5857.4, 9086.7) | (N=116)<br>24363.10<br>(20088.5, 29547.3) |
| 9-11 weeks | (N=110)<br>48.79<br>(39.6, 60.1) | (N=87)<br>7492.98<br>(5885.1, 9540.2) | (N=106)<br>34754.10<br>(30287.2, 39879.8) |
| ≥12 weeks | (N=154)<br>52.98<br>(44.4, 63.2) | (N=152)<br>8618.17<br>(7195.4, 10322.3) | (N=154)<br>63181.59<br>(55180.1, 72343.4) |

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence interval; S = Spike [a] Immune response evaluated using a multiplex immunoassay

The immune response observed in participants with one or more comorbidities was consistent with the overall population.

High seroconversion rates were observed in older adults (≥65 years) after the first SD (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second SD (100.0% [N=111, 95% CI: 96.7; NE]). The increase in S-binding antibodies was numerically lower for participants ≥65 years old (28 days after second SD: Geometric mean titre (GMT)=20,727.02 [N=116, 95% CI: 17,646.6; 24,345.2]) when compared to participants aged 18-64 years (28 days after second SD: GMT=30,695.30 [N=703, 95% CI: 28,496.2; 33,064.1]).

In participants with serological evidence of prior SARS-COV-2 infection at baseline (GMT=13,137.97 [N=29; 95% CI: 7,441.8; 23,194.1]), S-antibody titres peaked 28 days after dose 1 (GMT=175,120.84 [N=28; 95% CI: 120,096.9; 255,354.8).

Spike-specific T-cell responses as measured by IFN-ɣ enzyme-linked immunospot (ELISpot) assay are induced 12 days after a first dose of COVID-19 Vaccine AstraZeneca. These do not rise further after a second dose.

## 5.2 PHARMACOKINETIC PROPERTIES

## 5.3 PRECLINICAL SAFETY DATA

## 6 PHARMACEUTICAL PARTICULARS

## 7 MEDICINE SCHEDULE

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