Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines

ACV 19 Minutes on Item 2.1

ChAdOx1-S

Product Name: COVID-19 vaccine AstraZeneca

Sponsor: AstraZeneca Pty Ltd

February 2021

TGA Health Safety Regulation

Contents

Submission details

Type of submission:	New biological medicine Provisional approval determination issued 9 October 2020
Product name:	COVID-19 Vaccine AstraZeneca
Active ingredient:	ChAdOx1-S[1] Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein (GP)
Submission number:	PM-2020-06115-1-2
Proposed dose form:	Solution for injection
Proposed strength:	5 x 10^{10} viral particles per 0.5 mL dose
Initial indication proposed by the sponsor:	COVID-19 AstraZeneca is indicated for active immunisation of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19)
Indication proposed by Delegate:	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 with official recommendations. The decision has been made on the basis of short term efficacy and safety data. Continued approval is dependent upon the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.
Proposed dosage:	Two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks after the first dose. For intramuscular (IM) injection only.

Documents submitted for ACV consideration

The ACV considered the following documentation:

Documents provided between 25 and 29 January 2021:

A1	Delegate - request for ACV advice and overview – 'Delegate's Overview'
A1a	EMA – EMA considerations on COVID-19 vaccine approval – dated 16 November 2020
A2	Sponsor - application letter - dated 27 November 2020
M3	TGA - Quality – product summary
M3c	TGA – Quality – draft consent for labels that do not comply with Labelling Order – as at 25 January 2021

[1] Interim name pending decision on Australian Approved Name. Also referred to as AZD1222.

M4 TGA - Nonclinical – summary and evaluation report
M5 TGA - Clinical - evaluation report
RMP TGA - Risk Management Plan (RMP) - evaluation report
RMPa Sponsor – European Risk Management Plan – draft dated 26 January 2021
RMPb Sponsor – Australian Specific Annex to the EU-RMP – dated 30 January 2021

Documents provided 1 February 2021:

A3 Sponsor – preACV response - response
A3a Sponsor – preACV response - adverse reactions update
A3b Sponsor – preACV response – comments on PI
A3c Sponsor – preACV response – overseas regulatory status
A3d Sponsor – preACV response – comments on overseas PI
A3e Sponsor – preACV response – unaudited summary of nonclinical reproductive toxicity study 490843
PI Product Information – clean and annotated – from preACV response
CMI Consumer Medicine Information – clean and annotated – from preACV response
OS EU European summary of product characteristics
OS UK UK information for healthcare professionals

Document provided early and superseded:

PI Product Information – clean – draft dated 23 December 2020 - clean version of annotated version Doc ID-004370127 v2

Overview by Delegate of the Secretary of the Department of Health

Delegate's summary of data

The Delegate provided the following summary their request for ACV advice:

- 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.
- There were a number of changes in the manufacturing process and protocol during the clinical study, which has led to significant heterogeneity and potential confounding factors.
- In addition, there was limited follow up time, and high risk populations such as the elderly and those with significant co-morbidities were under-represented in the studies.
- Dosing interval varied from 3 to 26 weeks.
- For the dose proposed for registration, the SDSD group, efficacy was 62% (95% CI: 40%, 76%).
- Apart from reactogenicity, there were no significant safety concerns.

Delegate's preliminary view

While a decision is yet to be made, at this stage the Delegate is inclined to approve the registration of the product.

If registration was approved, the Delegate proposes the following additional conditions of registration:

Quality:

To be determined, depending on what data are submitted within the next few weeks

Nonclinical:

To provide the following clinical studies to the TGA when they are available

1. The ongoing distribution study with AZD1222
2. The ongoing reproductive toxicity with AZD1222

Clinical:

1. Changes to the product information
2. That the sponsor provide the full study reports of COV001, COV002, COV003 and COV005 when available in 2022
3. That the sponsor provide the interim and full study report for D8110COV00001
4. That the studies in the pharmacovigilance (PV) plan be included in the clinical study plan and be submitted prior to full registration.

RMP:

To be confirmed but will include

1. Monthly safety updates
2. Submission of studies in the PV plan
3. Inclusion of use in the elderly and long term safety in the missing information section of the summary of safety concerns.

Advice sought by Delegate

The ACV advised the following in response to the Delegate's specific request for advice:

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 complied 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 efficacy acceptable for the aims of the Australian immunisation program?
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 Product Information (PI) in relation to use in the elderly and advise if there is a need for stronger wording.
3. In post hoc secondary subgroup analysis, greater immunogenicity and efficacy was observed with longer dose intervals. Is there a scientific rationale for this?
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?
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 pregnancies are not yet known. Currently the use in pregnancy section states 'use in pregnancy is not recommended'. Is this adequate?

ACV discussion

Epidemiology

The first confirmed death from COVID-19 disease was in Wuhan, China in January 2020. There is an unmet need for safe and effective COVID-19 vaccines during the current public health emergency, declared to be a pandemic on 11 March 2020.

Australia is currently a low SARS-CoV-2 virus transmission environment, however case numbers could rise rapidly at any time.

International regulatory status

This vaccine has been authorised for temporary supply by the UK's MHRA in December 2020.

The EMA approved provisional registration on 29 January 2021, for use in person 18 years and older.

The vaccine, named 'Covain', is registered in India following transfer of technology and local manufacture by Serum Institute of India.

Applications are being assessed by Health Canada, Switzerland, and Singapore.

Efficacy

The 4 clinical studies differed in location (and so also background rates at the times of commencement and throughout the study, health care systems, manufacturing site of vaccine, control vaccine) and use of single doses and low dose (LD) first doses. The varying intervals between doses 1 and 2 were driven by logistical constraints.

Efficacy data in patients with comorbidity were limited: these trial participants were mainly under 55 years of age, and data on participants with HIV has not yet been reported. There was no difference in antibody responses in patients with or without co-morbidities.

In participants without serological evidence for SARS-CoV2 at baseline, S- binding and neutralising antibodies peaked after the second dose. In participants with serological evidence of prior SARS-CoV-2 infection at baseline, S-binding antibody levels peaked 28 days after dose 1 (n=28).[2]

The GMTs for S-binding and neutralising antibodies were lower in adults > 65 years of age in the clinical studies. When stratified by dosing interval, immune response in adults > 65 years of age was similar to that in younger people.

Secondary endpoints included efficacy against severe disease and hospitalisation, efficacy after a single dose, and efficacy against asymptomatic disease. The study was not powered for these endpoints, however a trend for lower numbers in the vaccine group was noted.

The ACV noted that the sponsor plans to submit the interim analysis data from an ongoing US/Peru/Chile Phase III study (D8110C00001) (n=32549). In this study, 25% of the enrolled population in the vaccine arm were over 65 years (n=5100). The dosing interval in this study is 29 days (range 26-36).

The final analyses of the studies in the meta-analysis will be available in Q2 2022.

Documentation released by other regulators mention different numbers of cases, reflecting different data lock points and maturing data. Information that appears

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949772/UKPAR_COVID_19_Vaccine_AstraZeneca_05.01.2021.pdf

inconsistent across regulators may become a point of public concern. Headline efficacy numbers ('62% effective') will change over time as studies with a longer period of follow up and in different patient populations emerge

There is currently no immunologic correlate of protection between antibody levels and prevention of COVID-19 disease. Evidence will accumulate on this point.

Safety

The safety analysis set included:

- 12021 participants who received at least one dose of ChAdOx1-S2
    - of these 68% (8266) received 2 doses
- median number of days of total exposure of 105 days
- median exposure after second dose of 62 days (range 0-131)(planned duration of follow-up 364 days)
- subjects aged 56-69 years (2694; 11.3%) and over 70 years (1460; 6.1%).

In the Oxford studies clinical trial participants, no new serious unexpected adverse events have been reported in the period 4 November 2020 to 27 January 2021. Since 17 January 2021, 2.3 million doses of ChAdOx1-S2 have been distributed in the UK.

The ACV noted that solicited local adverse events were more common after the first dose (any severity 71.3% of participants) than after the second dose (47.3%). The most common unsolicited adverse events were pain at injection site, headache, and pyrexia.

The ACV noted that experience with other chimpanzee adenovirus vector vaccines is limited. Previous clinical trials for a ChAdOx1 vectored vaccine have included influenza, tuberculosis, prostate cancer, malaria, and MERS-CoV. However, none of these vaccines have regulatory approval. In the small number of participants across trials, there were no associated safety concerns other than anticipated reactogenicity events.

The ACV noted that there is negligible risk for integration of adenovirus into the human genome. In addition, chimpanzee adenoviruses are not known to cause pathological illness in humans.

Neurological adverse events

The ACV noted one report of transverse myelitis occurred in clinical trials, leading to a pause in a trial. From the limited information available, the ACV viewed the event as unlikely to be related to be vaccine.

The background rates of myelitis in the Australian population need to be considered in post-market surveillance.

Post-vaccine myelitis has been noted with other vaccines.[3]

Bell's palsy has been reported in 3 subjects in ChAdOx1-S2 groups (3 months post-vaccination; 80 days after vaccination; and 2 days after vaccination) and 3 subjects in control groups.

Use in pregnancy

The ACV acknowledged that there is a lack of human data with regards to this vaccine in pregnant women (10 pregnancies in the ChAdOx1-S2 group, most with outcomes not yet known), and nonclinical data are incomplete.

[3] Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. Semin Neurol. 2008 Feb;28(1):105-20. doi: 10.1055/s-2007-1019132.

There is now evidence of transfer of maternal IgG antibodies to infant following maternal COVID-19 asymptomatic and symptomatic infections during pregnancy.[4]

Pregnancy increases the risk of severe COVID-19 disease.[5] The decision to vaccinate pregnant women relies on the individual benefit-risk assessment for each patient and should be as an informed shared decision between the patient and the clinician. This includes decisions on the administration of the second dose when the pregnancy is confirmed after the first dose.

Hyperthermia is a recognised teratogen, associated with miscarriage, neural tube defects, CNS anomalies and orofacial defects. Fever occurred in 7.9% of the vaccine group (1.2% of control group). Paracetamol (Use in pregnancy Category A) did not appear to significantly relieve fever following vaccination.

Members were aware of public domain decision making aids for other COVID-19 vaccines[6]; targeted clear communications will be needed for pregnant women and women considering pregnancy and their healthcare practitioners.

The ACV discussed the traditional approach in vaccine clinical trials of the exclusion of pregnant women and breast feeding women, and whether this is still best practice.[7]

While there is little plausible risk for the infant from breastfeeding, there is a biologically plausible benefit of vaccination of the mother in terms of passive immunisation with passage of antibodies and activated T cells into milk.

Use in older people

The ACV noted there were an insufficient number of cases in participants aged > 55 years to make any meaningful analysis of the results for efficacy in that cohort. It is not yet possible to provide a headline efficacy result for this group.

The ACV discussed the effects of the ageing immune system on the efficacy of vaccines.

The ACV noted:

- lack of nonclinical data in ageing animals
- humoral immunogenicity is not a very informative surrogate of efficacy in old age
- interferon-gamma is a more meaningful surrogate; GMT trended towards a lower response in those >65 (n=53; table 28 of clinical evaluation report)
- anti-ChAdOx1 antibody was not reported.

The ACV noted that the frail elderly are more likely to present with non-specific events such as falls or delirium as adverse events following immunisation. The prevalence of global health outcomes (hospitalisation, mortality) following vaccination also needs to be considered.

On balance, the ACV was of the view that at this time limiting the upper age in the indication was not in the best interest of public health or individuals, subject to potential benefits over risks, noting the heterogeneity of populations aged over 55 years and over

[4] Flannery DD, Gouma S, Dhudasia MB, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. *JAMA Pediatr.* Published online January 29, 2021. doi:10.1001/jamapediatrics.2021.0038

[5] https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm?s_cid=mm6925a1_w#T2_down

[6] https://foamcast.org/wp-content/uploads/2020/12/Vaccine-Info-for-Pregnant-People-track-changes-Updated-12-28.pdf

[7] Krubiner CB, Faden RR, Karron RA, Little MO, et al. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. Vaccine. 2021 Jan 3;39(1):85-120. doi: 10.1016/j.vaccine.2019.01.011. Epub 2019 May 3.

65 years. The ACV recommended it was preferable to manage any differential efficacy in this population through program delivery rather than registration.

There is currently no immunologic correlate of protection between antibody levels and prevention of COVID-19 disease. Evidence will accumulate on this point, for different populations including older people.

Risk Management Plan

The ACV noted the clinical trials were powered to detect adverse event to a rate of 1 event in 3300 recipients.

The pharmacovigilance plan is to be amended to include 'use in older people' as an Australia-specific area of missing information.

The ACV noted that currently the imbalance of cardiovascular serious adverse events (angina, chest pain) did not reach statistical significance.

The ACV recommended that vaccinations errors be monitored; compared to recent vaccination practices there may be errors related to mass immunisation using multi-dose vials (less experienced staff; changes to usual protocols, technology and documentation; monitoring of cumulative storage times under different conditions) and miscommunications (exacerbated by personal protective equipment).

The ACV noted that the sponsor will be providing regular (monthly) reporting to the TGA of additional safety data, not efficacy data.

The ACV noted that investigator-initiated studies will contribute to the literature reviewed in periodic safety reviews, for example, studies on mixed schedules of different brands of vaccine, and new virus strains.

Adverse events should be stratified by age and a validated frailty scale. Pharmacovigilance should address the prevalence of specific solicited adverse events, adverse events of particular concern in older people, and global health outcomes. Active surveillance in older people is needed, as there is less recognition of, and spontaneous reporting of, post-vaccination events/illnesses in older persons, especially the frail elderly. Pharmacovigilance activities should include population level analyses of falls, delirium, hospitalisation and mortality pre- and post- vaccine using routine data.

The ACV noted the unresolved issue of follow-up questionnaires to be used by the sponsor and reporter in relation to adverse events appearing in the summary of safety concerns. Members commented that clinicians may prefer follow-up forms that are not exclusive to a sponsor.

General comments

The ACV noted that the vaccine, if approved, will be the first vaccine in Australia containing a genetically modified organism. The Office of the Gene Technology Regulator is in the process of forming its opinion and determining licence conditions for the supply of the vaccine. Members asked that clear instructions be provided on the disposal of used vials and syringes and spillage, noting that the vaccine will be administered in a variety of settings.

The ACV noted that women will seek advice on whether to have a COVID-19 vaccine prior to conception.

People may be confused by the later and wider time interval of 4 to 12 weeks for the second dose, compared to another COVID-19 vaccine.

The ACV noted the absence of information on safety, immunogenicity and efficacy of co-administration of the COVID-19 Vaccine AstraZeneca with other vaccines (in particular, seasonal influenza vaccines), and interactions for people taking immunosuppression therapies.

The ACV noted that recombinant adenovirus is propagated and manufactured using T-Rex-293 host cell line, derived from human embryonic kidney cells (HEK293 cell line). This may become a point of public interest.

ACV advice to the Delegate

The ACV advised the following in response to the Delegate's specific request for advice:

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 complied 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 efficacy acceptable for the aims of the Australian immunisation program?**

The ACV advised that, based on data currently available, the vaccine has acceptable efficacy for the proposed provisional approval.

The ACV advised that, if approved, the COVID-19 Vaccine AstraZeneca can be available to be used within the Australian Government COVID-19 Vaccine and Treatment Strategy, subject to relevant clinical and programmatic guidance.

The ACV noted that program implementation ('official recommendations' in the proposed indication) will consider all available vaccines, including preferential use of different vaccines in different groups of Australians such as frail older people, supply issues, etc.

The ACV noted the lack of data on the balance of benefits and potential harms in pregnant women, those with autoimmune/inflammatory diseases, immunocompromised, older people (particularly those with frailty) and those with severe or unstable comorbid medical conditions. There was also insufficient data to assess efficacy in individuals over 55 years of age, noting that the vaccine was immunogenic in this age group (discussed further in Question 2).

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 Product Information (PI) in relation to use in the elderly and advise if there is a need for stronger wording.**

There was much discussion around use in older people. The ACV agreed with the proposed indication of use in adults 18 years and above with no upper age limit.

Available safety data indicate that local and systemic adverse events are milder and reported less frequently in older adults (> 65 years) compared to younger adults.

It was noted that in frail older people, adverse events may be atypical (e.g. falls) and mild disturbances in physiological homeostasis may be clinically significant.

The ACV advised that the limitations of the data in older persons should be clearly expressed in the PI. The ACV generally agreed with the proposed wording in the PI, which describes the limitation of data demonstrating efficacy in the population over 55 years of age, and limited data on safety in this age group, particularly in those over 65 years of age.

Immunogenicity studies demonstrate older participants produce similar or in some cases moderately lower immune responses compared with younger participants. However, there is no immunologic correlate of protection and it is not possible to predict what level

of efficacy will be provided for older adults in the absence of further data in this population.

Administration of the vaccine will not negate the need for older people and those around them to follow current precautions and public health guidance to reduce the risk of acquiring COVID-19.

The ACV noted that further interim analysis data from a Phase III study containing higher numbers of older participants, who will also have co-morbidities, is expected to be provided to the TGA in Q2 2021.

The ACV noted that the Australian Technical Advisory Group on Immunisation (ATAGI) and the Department of Health will be providing clinical guidance on the use of this vaccine under the Australian Government COVID-19 Vaccine Program which will include information on the available data, risks and benefits of vaccination in subgroups, including in older people.

The ACV discussed the importance of collecting specific post-market data about risks to frail older people, from routine and other sources The ACV advised that post-market data should be stratified by frailty (e.g. community-dwelling vs nursing home residents) and should include adverse events specific to this group (e.g. falls, delirium).

3. In post hoc secondary subgroup analysis, greater immunogenicity and efficacy was observed with longer dose intervals. Is there a scientific rationale for this?

The ACV advised a longer dose interval between the first and second doses allows for affinity maturation of the T cell responses which will improve long term B cell responses. A longer interval – that is, closer to 12 weeks, rather than 4 weeks – will allow the second dose to act as a true booster to increase immunogenicity and was associated in post-hoc analysis with a trend toward higher vaccine efficacy following the second dose (see also Question 4).

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?

The ACV supported the provision of relevant information in a brief statement, noting that there are challenges in interpreting data and varying statistical robustness within the interim dataset.

Information on variation in dose interval should not detract from the key message of the importance of the second dose.

The ACV acknowledged that a longer interval (around 12 weeks) between doses was associated with a trend towards higher levels of antibody post dose 2 and a possible modest increase in efficacy. However, this was based on post hoc secondary subgroup analysis, and confirmatory data may not become available. The ACV also noted that, while again a post-hoc analysis, the short-term efficacy following one standard dose (prior to receipt of a second dose) was approximately 60%.

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 pregnancies are not yet known. Currently the use in pregnancy section states 'use in pregnancy is not recommended'. Is this adequate?

The ACV advised that the PI section on Use in Pregnancy should also state:

- use in pregnancy is not routinely recommended, due to the lack of data and as a precautionary measure

- use of the vaccine is not contraindicated
- as a replication deficient viral vaccine, pregnant women may choose to receive this vaccine in consultation with their antenatal clinician if they are at increased risk of the disease.

The ACV recommended the sponsor give consideration to the inclusion of Australian women in the pregnancy registry.

6. Other advice

The ACV advised that sufficient and appropriate information should be provided to clinicians and patients to allow decision making on benefit and risks, given current uncertainties.

The risks of vaccination to a breastfeeding woman appeared minimal. Breastfeeding women can be offered vaccination if they are at increased risk e.g. healthcare workers.

The ACV recommended the sponsor give consideration to a co-administration study with 2021 Southern Hemisphere influenza vaccines.

The ACV advised vaccination errors should be monitored in post-market surveillance.

The PI will be an important source of information. ATAGI and other bodies will also be developing information.

ACV conclusion

The ACV considered COVID-19 vaccine AstraZeneca to have an overall positive benefit-risk profile, and therefore support provisional approval for the following:

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 with official recommendations.

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

Ratified and sent to the sponsor on 19 February 2021.

Therapeutic Goods Administration

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