AZD1222 vaccine against COVID-19 developed by Oxford University and Astra Zeneca: Background paper

DRAFT

Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines

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Background

Replication-deficient adenovirus vectors containing a pathogen-specific transgene have been used as novel vaccines because of their ability to induce strong humoral and cellular responses. However, pre-existing immunity might reduce the immunogenicity of vectors derived from human viruses, hence, use of simian adenoviruses might be preferable. COVID-19 Vaccine AstraZeneca, also known as AZD1222 or ChAdOx1-S (recombinant), was developed by the Oxford University, United Kingdom, and Astra Zeneca, and is a replication-deficient chimpanzee adenovirus-vectored vaccine expressing the full-length SARS CoV-2 spike glycoprotein gene.

Characteristics of AZD1222 vaccine against COVID-19

AZD1222 vaccine is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1-S (recombinant)) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Adenoviruses are non-encapsulated, icosahedral particles (virions), and contain a single copy of the double-stranded DNA genome. The expression cassette for the SARS-CoV-2 spike protein fused to the tissue plasminogen activator (tPA) leader sequence uses a modified human cytomegalovirus (CMV) promoter and a bovine growth hormone polyadenylation sequence.

The following information is derived from the Product Information by the European Medicine Agency`s Committee for Medicinal Products for Human Use (CHMP)[1]:

Composition

One dose (0.5mL) contains ChAdOx1-S (recombinant) 5 x 10^{10} viral particles.
The vaccine is produced in genetically modified human embryonic kidney (HEK) 293 cells.
In addition to ChAdOx1-S (recombinant), this product also contains the excipients L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injections.
None of the excipients are of animal or human origin. The excipients are well established for pharmaceutical products.

Stability

Proposed shelf-life of 6 months for the drug substance.

Shelf-life

Chemical and physical in-use stability have been demonstrated from the time of vial opening (first needle puncture) to administration for no more than 48 hours in a refrigerator (2-8Degrees Celsius). Within this time period the product may be kept and used at temperatures up to 30 Degrees Celsius for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

Drug product description

The product is a colourless to slightly opalescent solution provided in a multidose vial. There will be different presentations available in different regions. The drug product is multidose vial with stoper (elastomeric with aluminum overseal).

Container

The drug product vials are packaged as 10 vials in a carton. There will be different presentations available in different regions. For example:
Presentations in EU:

- 4 ml (8-dose) vials
- 5 ml (10-dose) vials

Presentations via COVAX:

- 5 ml (10-dose) vials

Serum Institute India (SII)'s Covishield is expected to be available in a number of presentations:

- 1 dose – 0.5 mL per vial
- 2 dose – 1.0 mL per vial
- 5 dose – 2.5 mL per vial
- 10 dose – 5.0 mL per vial
- 20 dose – 10 mL per vial

Pharmacokinetics

Two biodistribution studies were performed which suggest that, after injection, the virus does not replicate, or persist, and does not biodistribute beyond the injection site in a way that would be clinically significant.

Reproductive and developmental toxicity

Both a dose-range study (study 490838) and the main GLP embryo-foetal development study (study 490843) were completed. In top-line results from main study (Study 490843), there were no test item-related effects seen for dams in-life including at the injection site, for female reproduction, fetal or pup survival, pup physical development and no abnormal gross pathology findings in pups prior to or post weaning or in dams in either phase. There were no test item-related foetal external, visceral or skeletal findings. The audited report is due in mid-February 2021.

Lactation

Considering potential use of this vaccine in women who are breastfeeding, there are no studies at this time to document safety. Studies are being planned to address these questions.

Pre-clinical studies

*Note: The following information is derived from scientific publications. Those publications used the term "*ChAdOx1-S (recombinant)" which is equivalent to AZD1222.

The efficacy of ChAdOx1-S (recombinant) was assessed in rhesus macaques. Six animals per group were vaccinated using a prime-only regimen (28 days before challenge) or a prime–boost regimen (56 and 28 days before challenge) intramuscularly with 2.5×10^{10} ChAdOx1-S (recombinant) virus particles each. As a control, six animals were vaccinated via the same route with the same dose of ChAdOx1-S (recombinant) green fluorescent protein (GFP) (one animal was vaccinated 56 and 28 days before challenge and five animals were vaccinated 28 days before challenge). No adverse events were observed after vaccination. Spike-specific antibodies were present as early as 14 days after vaccination and were significantly increased after the second immunization (two-tailed signed-rank Wilcoxon test). Endpoint IgG titres of 400–6,400 (prime) and 400–19,200 (prime–boost) were measured on the day of challenge. Virus-specific neutralizing antibodies were also significantly increased after secondary immunization (two-tailed signed-rank Wilcoxon test) and detectable in all vaccinated animals before challenge (5–40 (prime) and 10–160 (prime–boost)), whereas no virus-specific neutralizing antibodies were detected in control animals. IgM antibodies were present in the serum after vaccination on the day of the challenge in six out of six prime–boost and two out of six prime-only animals SARS-CoV-2 spike-specific T cell responses were detected on the day of challenge by IFNγ ELISpot assay after the stimulation of peripheral blood mononuclear cells with a peptide library that spanned the full length of the spike protein. No statistically significant difference in the magnitude of the response was found between the prime–boost and prime-only group (Mann–Whitney *U*-test, $P = 0.3723$). As previously reported[6], vaccination with ChAdOx1-S (recombinant) resulted in the induction of neutralizing antibodies against the vaccine vector itself within 28 days of vaccination. Nonetheless, a boost vaccination with ChAdOx1-S (recombinant) resulted in a significant increase in binding and neutralizing antibodies in NHPs and an increase in the SARS-CoV-2 virus-neutralizing titre was not significantly correlated with the ChAdOx1-S (recombinant) virus-neutralizing titre (two-tailed Pearson correlation, $r^2 = 0.6493$ $P = 0.0529$).

A post-vaccination SARS-CoV-2 challenge in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated enhanced respiratory disease (VAERD)[2]. Clinical disease score in monkeys was reduced, and the vaccine prevented damage to the lungs. A prime-boost regimen induced humoral immune responses. Viral loads were reduced in the lungs, but there was no reduction in viral shedding from the nose with either prime-only or prime-boost regimens. These suggest that ChAdOx1-S (recombinant) may not prevent infection nor transmission of SARS-CoV-2, but it may reduce illness. The immune responses were not skewed towards a Th2-type and there was no suggestion of enhanced disease following vaccination. Whilst a single dose induced antigen-specific antibody and T cells responses, a booster immunisation enhanced antibody responses, particularly in pigs, with a significant increase in SARS-CoV-2 neutralising titres[3].

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine is derived from four ongoing studies:

- COV001, a Phase 1/2 trial conducted in the UK
- COV002, a Phase 2/3 trial conducted in the UK
- COV003, a Phase 3 trial conducted in Brazil, and
- COV005, a Phase 1/2 trial conducted in South Africa.

Smaller trials using the vaccine are planned or ongoing in other countries, including South Africa, Kenya, Russia, Japan and India. In addition, a large phase 3 trial involving about 30,000 participants is ongoing in the US, Peru, Chile, Columbia and Argentina, and interim results from this trial are expected shortly.

The primary analysis of vaccine efficacy of COVID-19 Vaccine AstraZeneca (AZD1222) against first SARS-CoV-2 virologically-confirmed COVID-19 in the standard dose (SD) SDSD Seronegative for Efficacy Analysis Set (any dosing interval) is included as the primary source of data for efficacy reported in this background document. Results were generated using the primary efficacy analysis data cut-off #2(DCO2) on 07 December 2020.' These data were made available to SAGE to review. Astra Zeneca has given permission for these data to be made public in this background paper.

Immunogenicity studies in humans

Study COV001[4-6]

1077 participants were enrolled of whom 543 were randomised to receive ChAdOx1-S (recombinant) and the rest received meningococcal group A,C,W and Y conjugate vaccine (MenACYW) as the control). Subsequently some ChAdOx1-S (recombinant) recipients received boosters at different doses and dose intervals. Binding antibody (ELISA) responses were consistently detected after one dose and substantially boosted following a second dose, correlating with neutralising antibody titres. The latter were measured using several methods and were detectable in 32/35 subjects after one dose and all after two, reaching titres similar to those in convalescent sera. Both CD4+ and CD8+ T cell responses were detected by ELISpot.

Antibody responses were predominantly of IgG1 and IgG3 subclasses, with low levels of IgG2 and little detectable IgG4, consistent with a Th1-biased response. Likewise, cytokine secretion from antigen-specific CD4+ T-cells showed a Th1-bias with increased IFN-gamma and TNF-alpha generation at day 7 and 14 rather than a Th2-bias (IL-4 and IL-13).

A standard dose (SD; 5×10^{10} viral particles (vp)) booster administered 56 days after the priming dose induced a rise in polyfunctional antibody concentrations[7]. These were higher than following low dose (LD; 2.2×10^{10} vp or 2.5×10^{10} vp) boosters but not significantly higher than following booster doses given at 28 days. These boosters did not measurably increase the magnitude of the T cell responses. While anti-adenoviral vector neutralising antibody responses were detectable, their presence was not associated with reduced antibody or T cell anti-SARS CoV2 responses to booster vaccine doses.

Booster doses[6]: Using a systems serology approach we also demonstrate that anti-spike neutralizing antibody titers, as well as Fc-mediated functional antibody responses, including antibody-dependent neutrophil/monocyte phagocytosis, complement activation and natural killer cell activation, were

substantially enhanced by a booster dose of vaccine. A full booster dose (SD) of vaccine induced stronger antibody responses than a dose-sparing half-dose (LD) boost, although the magnitude of T cell responses did not increase with either boost dose. A booster dose of ChAdOx1-S (recombinant)is safe and better tolerated than priming doses.

StudyCOV002[7]:
In the first part of this phase 2/3 trial, 560 subjects, in three different age groups(18-55, 55-69 and >70 years) were enrolled and received either one (older two groups only) or two doses of ChAdOx1-S (recombinant) or MenACWY (control) vaccine, 28 days apart. Two dose regimens were used, one with a low dose (LD) and the other with a standard dose (SD).
The median anti-spike SARS CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts, and likewise, the neutralising antibody titres. T-cell responses peaked at day 14 after a single SD and did not increase significantly after the boost vaccination.
The antibody response tended to be slightly lower with the LD regimen compared to the SD regimen at day 56.
The rate of seroconversion (> 4-fold increase from baseline) to S-binding antibodies was > 98% at 28 days after the first dose and >99% at 28 days after the second dose for participants seronegative at baseline. The rate of seroconversion with a live neutralisation assay was high (>80%) at 28 days after the first dose and >99% at 28 days after the second dose for participants seronegative at baseline.
ChAdOx1-S (recombinant) appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a booster dose[7].

In the COV002 study, some participants assigned to receive SD priming and booster doses in fact received a lower than intended priming dose (roughly equivalent to the LD given during the phase 2 part of the study). The interval between priming and booster doses for all these LDSD subjects was also longer than initially foreseen; about 12 weeks. Among subjects who received SD priming and booster doses ("SDSD"), there was a range of dose intervals, mostly ranging between 4 and 12 weeks. In this group, observed immunogenicity (by immunoassay)[8] following the booster dose increased with longer dose interval. Immunogenicity was similar among those given the lower priming dose with a longer dose interval and among those given the standard priming dose with a longer dose interval.

Efficacy

Note: *The efficacy analysis reported in this document reflects data from DCO2 (7 December 2020) from all four studies, including patients that received two standard doses (SDSD) with any interval between doses (ranging from 3 to 23 weeks (21 to 159 days))*

The primary analysis of vaccine efficacy of COVID-19 Vaccine AstraZeneca includes data from all four studies: COV001, COV002, COV003, and COV005:

COV001 (UK; Phase I/II): This is an first in human study in adults 18-55 years of age, designed to evaluate various dosing regimens, involving single dose or a 2-dose regimen of AZD1222 or MenACWY. different dose levels (SD and LD), and various dosing schedules.

COV002 (UK; Phase II/III): This study enrolled participants from 19 study sites and targeted individuals working in professions with high possible exposure to SARS-CoV-2, such as health and social care settings. This study began by enrolling participants aged 18 to 55 years. Only one vaccine dose was planned initially but this was increased to two on the basis of immunogenicity findings in Phase 1/2 studies (COV001). Participants over 55 years of age were also enrolled subsequently and had a shorter interval between their first and second doses. Participants received a single dose or a 2-dose regimen of AZD1222 vaccine or MenACWY. Most participants had an interval between doses of 4 to 12 weeks and about 20% had an interval in excess of this.

COV003 (Brazil; Phase III): This study enrolled participants at high risk of exposure to the virus, including healthcare workers, in 6 sites across the country. Recruitment of participants in Brazil began a little later than the COV002 (UK) study and they were offered two doses of the vaccine up to 12 weeks apart (target 4 weeks). Participants receive 2 doses of AZD1222 or MenACWY (first dose)/saline placebo (second dose). For less than 2% of participants, the interval between doses was more than 12 weeks.

COV005 (South Africa; Phase I/II): This study enrolled adults living with and without HIV at 7 sites in the country. The study in South Africa started at approximately the same time as the study in Brazil; participants received 2 doses of AZD1222 vaccine or saline placebo at a dose interval between less than 4 weeks to 12 weeks. There were no doses administered more than 12 weeks apart in the study in South Africa.

Women who were pregnant or breast-feeding were excluded from all studies.

Baseline demographics were well balanced across the vaccine and control treatment groups. In the pooled analysis, among the participants who received the vaccine DCO2 (7 December 2020) from all four studies, including patients that received two standard doses (SDSD) with any interval between doses, 90.2% of participants were 18 to 64 years old (with 9.8% aged 65 or older); 54.4% of subjects were female; 71.8% were White, 11.8% were Black and 3.4% were Asian. 2,592 (36.0%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m2, cardiovascular disorder, respiratory disease or diabetes).

The primary analysis of the trial results was conducted when participants had been followed for a median of 133 days after the first dose and 80 days after the second vaccine dose.

Efficacy against Covid-19

The primary endpoint was specified as efficacy against symptomatic Covid-19 at greater than or equal to 15 days after the second dose among participants who were seronegative at trial entry. 14,380 participants were eligible for inclusion in the efficacy analysis (43% UK, 47% Brazil, 10% South Africa) among whom there were 271 Covid-19 cases with onset ≥ 15 days post dose 2, with 74 cases in the vaccinated group and 197 in the control group with the estimate of vaccine efficacy (VE) being 63.09% (95% confidence interval (CI) 51.81 to 71.73).

Only about 9.8% of participants were aged 65 years or older and among these there were only 12 cases of Covid-19, 4 in the vaccine groups and 8 in the control group (VE = 51.91%; 95% CI -59.98% to 85.54%), based on >= 15 days after the second dose of vaccine (7 December 2020 data cut).

Exploratory analyses were conducted of vaccine efficacy >= 15 days after the second dose according to the interval between the first and second doses. For about 59% of participants the interval was 4-8 weeks, 22% 9-12 weeks and 16% more than 12 weeks. The estimates of VE increased significantly in these 3 groups, being 56%, 70% and 78% respectively.

In the first 21 days after the first dose there was no difference in Covid-19 incidence between vaccine and control groups. From 22 days after the first dose up to the time of the second dose or up to 12 weeks after the second dose there were 18 cases of Covid-19 in the vaccine group and 63 cases in the control group (VE=71.42% 95% ; CI (51.11, 84.08)). The interval between first and second doses varied but up to 12 weeks there was no evidence of a decline in efficacy.

Efficacy against Covid-19 hospitalisation (WHO clinical progression scale ≥4)

In the total trial population, there were 24 cases of hospitalised Covid-19, 2 in the vaccine group and 22 in the control group. The corresponding numbers in the periods at any time from ≥22 days after the first dose were 0 in the vaccinated group and 14 in the control group. For the period from 15 or more days after dose 2 were, respectively, 0 and 8 hospitalized cases.

Efficacy against severe Covid-19 (WHO clinical progression scale ≥ 6)

In the total population, there were only 3 cases of severe COVID-19, all in the control group.

Summary

Evidence of efficacy emerged from about 22 days after the first vaccine dose. The vaccine was efficacious against laboratory-confirmed Covid-19 from 22 days after the first dose and persisted until at least 12 weeks until a second dose was given (VE=71.42%). The primary trial endpoint was efficacy measured more than ≥15 days after the second vaccine dose until the end of the data date cutoff, which was, on average, about 2 months (mean 58 days; median 66 days) after the second dose and during this period the vaccine continued to be efficacious (VE=63.09%). Exploratory analyses indicated that efficacy following the second doses increased with increasing intervals between the first and second doses.

A relatively small proportion of participants were aged 65 years or over and the number of cases of Covid-19 in this age group was too small to assess protection based on the efficacy data alone. There were no cases of Covid-19 hospitalisation, severe COVID-19 disease, or Covid-19 death in participants with ≥65 years of age who received AZD1222.

A summary of the main findings are presented in Table 1:

Table 1 Vaccine Efficacy for Incidence of First SARS-CoV-2 Virologically-confirmed COVID-19 Occurring ≥ 15 Days Post Second Dose in the SDSD for Efficacy Analysis Set (Any Dosing Interval) Overall and by Subgroup (COV001 + COV002 + COV003 + COV0

Analysis set Subgroup	Participants with events AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD for efficacy analysis set, any dose interval					
Overall [a]	74 / 7201 (1.03)	197 / 7179 (2.74)	63.09	(51.81, 71.73)	<0.001
Age subgroup [b]					
≥ 65 years	4 / 703 (0.57)	8 / 680 (1.18)	51.91	(-59.98, 85.54)	0.233
18-64 years	70/6498 (1.08)	189/6499 (2.9)	63.47	(51.95;72.23)	<0.001
Presence of comorbidity at baseline [b, c]					
Yes	28 / 2516 (1.11)	75 / 2540 (2.95)	61.87	(41.15, 75.29)	<0.001
No	46 / 4309 (1.07)	115 / 4227 (2.72)	61.62	(45.98, 72.73)	<0.001
Gender [b]					
Male	24 / 3285 (0.73)	82 / 3237 (2.53)	71.34	(54.85, 81.81)	<0.001
Female	50 / 3916 (1.28)	115 / 3942 (2.92)	56.97	(40.04, 69.12)	<0.001
Country [b]					
United Kingdom	23 / 3048 (0.75)	82 / 3136 (2.61)	71.70	(55.07, 82.17)	<0.001
Brazil	49 / 3414 (1.44)	112 / 3339 (3.35)	57.61	(40.73, 69.68)	<0.001
South Africa	2 / 739 (0.27)	3 / 704 (0.43)	37.13	(-276.69, 89.51)	0.611
Time interval between Dose 1 and Dose 2 [b]					
≥ 4 to 8 weeks	54 / 4796 (1.13)	117 / 4662 (2.51)	56.42	(39.86, 68.43)	<0.001
9 to 12 weeks	11 / 1053 (1.04)	39 / 1101 (3.54)	70.48	(42.41, 84.87)	<0.001
> 12 weeks	8 / 1146 (0.70)	38 / 1213 (3.13)	77.62	(51.98, 89.57)	<0.001

Safety

Note: *The safety analysis reported in this document reflects data from DCO1 (data cut at 4 November 2020)*

The overall safety of the AZD1222 vaccine is based on an interim analysis of pooled data from four clinical trials:

2 trials conducted in the United Kingdom (phase I/II and phase II/ III), 1 in Brazil (phase III), and 1 in South Africa (phase I/II). At the time of analysis, safety data was available from 23,745 participants

≥18 years old, who had been randomized and received either the vaccine or control. Out of these, 12,021 subjects received at least one dose of the vaccine, and 8,266 received two doses.

At the time of analysis the median follow up time post-dose 1 was 105 days in the AZD1222 group and 104 days in the control group. .

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.

Adverse reactions

The majority of the adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and less frequent. Reactogenicity was generally milder and less frequent in older adults (≥65 years old) compared to younger adults (18-64 years). Analyses of safety data by age, comorbidity, baseline seropositivity and country did not raise any specific concerns.

The most frequently reported adverse reactions were injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (includes feverishness (33.6%) and fever >38°C (7.9%)), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). The incidence of subjects with at least one local or systemic solicited event after any vaccination was highest on day 1 following vaccination, decreasing to 4% and 13 %, respectively, by day 7. The most common systemic solicited AEs at day 7 were fatigue, headache and malaise.

- Very common (≥ 10%, may affect more than 1 in 10 people): headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia (including feverishness – very common, and fever ≥ 38° - common), chills

- Common (≥ 1% to < 10%, may affect up to 1 in 10 people): injection site swelling, injection site erythema

Safety data is limited in older subjects, particularly those ≥ 65 years. The frequency and severity of the solicited adverse events was lower in subjects ≥ 65 years, and the incidence of SAE and AESI was similar between <65 and ≥ 65 years. There was no clinically relevant difference seen in the larger population of subjects that had at least one comorbidity.

Adverse Events of Special Interest (AESI)

Neuroinflammatory events

A very small number of neuroinflammatory events have been reported following vaccination
A causal relationship has not been established.

Neurological cases of interest

A new diagnosis of multiple sclerosis was seen in the vaccine arm. Symptom onset was 10 days after the first dose. An MRI of the brain and spinal cord demonstrated multiple lesions. All but one of these lesions were not gadolinium-enhancing suggesting that most lesions pre-dated the vaccine dose. A likely case of 'short segment inflammatory myelitis' was seen in the vaccine arm, although the diagnosis is not certain. The symptom onset was 14 days after the second vaccine dose. Based on the available data, a causal association between the vaccine and the two cases cannot be concluded with certainty.

A case of 'transverse myelitis' was seen in the control group. The symptom onset was 54 days after the first control dose. Two cases of trigeminal neuralgia were seen in the control group.

Facial palsies

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

'Neuroinflammatory conditions' is included in the RMP as an important potential risk and will be closely monitored by routine and additional pharmacovigilance activities.

Serious Adverse Events (SAEs)

Five SAEs were considered related by the investigator, of which two were in the vaccine group (pyrexia, and transverse myelitis) and three were in the control group (autoimmune haemolytic anaemia, C-reactive protein increased and myelitis)

Special Considerations

Pregnancy

Pregnancy was reported for 21 subjects; 12 in the vaccine and 9 in the control group. 5 cases ended in spontaneous abortion – 2 in the vaccine and 3 in the control group.

Animal studies of potential toxicity to reproduction and development have not been completed. Preliminary preclinical studies do not indicate harmful effects on fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

A pregnancy sub-study, and pregnancy registry are planned.

Administration of vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Paediatric population
No data is available in subjects less than 18 years of age.

Immunosuppression

No data is currently available in immunocompromised subjects including those receiving immunosuppressant therapy. The efficacy of the vaccine may be lower in immunosuppressed individuals. Safety data is awaited in a subgroup of HIV positive subjects.

Safety related to vaccine interactions

No data are available on use of the vaccine with concomitant vaccines, including influenza vaccines. Licensed seasonal influenza and pneumococcal vaccinations were permitted at least 7 days before or after the study vaccine.

Considerations for vaccinating older adults (age ≥ 65 years)

Vaccine efficacy in older adults aged ≥65 years is uncertain, because only 9.8% of the trial participants were 65 or older. This sample size was too small to estimate vaccine efficacy in this age group with precision given that the attack rate in this age group was lower (e.g., due to shielding behaviours). Only 8 cases in the control arm and 4 cases in the vaccine arm were observed >= 15 days after the second dose of vaccine based on the 7 December 2020 data cut, yielding a vaccine efficacy of 51.91% (95% CI: -59.98 to 85.54%). Efficacy was observed starting from day 22 after the first dose. While a longer interval between doses increased efficacy and immunogenicity, such data are not available for older persons as most older persons received a shorter inter-dose interval of 4-6 weeks. No cases of COVID-19 requiring hospitalisation were recorded among those receiving 2 doses of the vaccine compared with 2 in the control group in this age group. Safety data from 1169 vaccine recipients in this age group indicate the vaccine is well tolerated with no concerning safety signals, although detection of rare outcomes will require continued safety monitoring during the ongoing phase 3 trials and programmatic use of the vaccine. Immunogenicity data from phase 1/2 studies indicates high seroconversion rates by S-binding antibodies after the first SD (97.8%) and the second SD (100%) in older adults, and T cell responses were comparable in older and younger age groups[3-7].
The majority of COVID-19 deaths globally have been among older adults aged 65+, as a result of an infection fatality rate that rises exponentially with age[9, 10]. Older adults are therefore identified as a priority population in the WHO SAGE Roadmap for Prioritising Uses of COVID-19 Vaccines in the Context of Limited Supply[11]. This prioritisation is supported by vaccine impact modelling work, including scenarios with substantially reduced vaccine efficacy in older adults[12].

Emerging Virus Variants of Concern

SARS-CoV-2 viruses undergo evolution. Some new virus variants may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.
AZD1222 was designed around the SARS-CoV-2 prototype virus identified in November 2019. The SARS-CoV-2 spike gene has accumulated mutations, including within the receptor binding domain (RBD) and N-terminal domains (NTD), which are major targets of the immune response. The RBD mutations include the N501Y mutation which is associated with increased affinity for the angiotensin converting enzyme-2 (ACE2); while the E484K and K417N RBD mutations and mutations in the NTD have been associated with neutralising antibody escape (13).

The N501Y.V1 (B.1.1.7) lineage, first identified in the United Kingdom (UK), included the N501Y mutation which has been associated with 53% increased transmissibly compared to earlier variants (14). The B.1.1.7 variant has further evolved to include the E484K mutation in the UK.

The N501Y.V2 (B.1.351) lineage first identified in South Africa contains three RBD and NTD mutations (L18F, D80A, D215G, R246I) and a three amino acid deletion from positions 242 to 244). Comparison of the sensitivity of B.1.351 relative to original lineage virus to neutralizing antibodies from convalescent donors infected with the original lineage virus using a spike-pseudotyped neutralization (PSVA) assay demonstrated 48% of sera were unable to neutralize B.1.351, with the rest showing 3 to 86-fold reduction in neutralization (15). This was corroborated using a live virus neutralisation assay (LVNA), with reduction in antibody activity ranging from 6-fold to knockout for the B.1.351 variant(16). A new variant of SARS-CoV-2, B.1.1.7, emerged as the dominant cause of COVID-19 infection in the UK from November 2020 with a transmission advantage over the previous variants of the virus.

A preprint of ongoing work to assess effectiveness of Oxford's ChAdOx1 coronavirus vaccine shows that AZD1222 vaccine has similar efficacy against the B.1.1.7 'Kent' coronavirus strain currently circulating in the UK to previously circulating variants (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160). The protection against symptomatic infection was similar despite lower neutralising antibody titres in vaccinated individuals against the B.1.1.7 variant than the 'Victoria' strain of virus, e.g. the original strain identified in Wuhan.

In the South African multi-site, randomised, double-blinded, placebo-controlled Phase I/IIa trial on safety and efficacy of AZD1222 vaccine in young healthy adults age 18 to <65 years, dose two serum samples (n=26) were tested by pseudotyped (PSVA) and live virus (LVNA) neutralisation assay for neutralization activity against the B.1.351 and D614G variant. At the time of writing, this analysis had not been peer-reviewed, and was only available as preprint. B.1.351 variant showed high resistance to vaccinee sera on the PSVA and LVNA. In the primary objective analysis, 23 (3.2%) of 717 placebo recipients and 19 (2.5%) of 750 vaccinees developed mild-moderate Covid-19; VE 21.9% (95% CI: -49.9; 59.8). Thirty-nine (92.9%) of the 42 primary endpoint cases were due to the B.1.351 variant; against which VE was 10.4% (95% CI: -76.8; 54.8).

Although this study indicates that AZD1222 vaccine does not protect against mild-moderate Covid-19 caused by B.1.351 variant, extrapolating from immunological insights, it may still protect against

severe Covid-19. Other vaccine induced immune mediators, such as Th1 dominated cell mediated immune responses including T helper cytotoxic CD8+ cells, may play a more central role in reducing the risk of severe Covid-19 rather than neutralizing antibodies alone.

Indirect evidence is compatible with protection against severe COVID-19, however, this remains to be demonstrated in ongoing clinical trials and post-implementation evaluations. These preliminary findings highlight the urgent need for a coordinated approach for surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor the situation; as new data become available, recommendations will be updated accordingly.

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Annexes

Note:
The annexes contain the grading of recommendations, assessment, development and evaluations – GRADE tables (Annex 1 to 6) and the SAGE evidence-to-recommendation framework tables – ETR tables (Annex 7-9). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Annex 1 GRADE table: Efficacy of AZD1222 COVID-19 vaccine in adults

Population : Adults (18–64 years)
Intervention: Two doses of AZD1222 vaccine
Comparison: Placebo/ active control
Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–64 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).**
	Conclusion			We are very confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–64 years).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.
[b] Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 2 GRADE table: Safety of AZD1222 COVID-19 vaccine in adults

Population : Adults (18–64 years)
Intervention: One or two doses of AZD1222 vaccine
Comparison: Placebo/ active control vaccination
Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/ active control in adults (18–64 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT (1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of AZD1222 vaccine in adults (18–64 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.
[b] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events (i.e. less than about 1/2000). These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination.

Annex 3 GRADE table: Efficacy of AZD1222 COVID-19 vaccine in older adults

Population : Older adults (≥65 years)
Intervention: Two doses of AZD1222 vaccine
Comparison: Placebo/ active control
Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/ active control in preventing PCR-confirmed COVID-19 in older adults (≥65 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[b]	-2
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the evidence indicating that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Of the trial participants, approximately 10% (n= 1380) were aged over 65 years. While supportive evidence (immunogenicity data in this age group) suggest that the vaccine elicits an immune response comparable to older adults, the trial did not show a statistically significant vaccine efficacy in this age-group. The very serious imprecision due to large confidence intervals and the limited sample size were considered as factors constituting a limitation that leads to downgrading of the evidence. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 4 GRADE table: Safety of AZD1222 COVID-19 vaccine in older adults

Population : Older adults (≥65 years)
Intervention: One or two doses of AZD1222 vaccine
Comparison: Placebo/ active control
Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/ active control in older adults (≥65 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT(1;3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events following one or two doses of AZD1222 vaccine in older adults (≥65 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.
[b] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events (i.e, about 1/250). These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination..
[c] Of the trial participants, approximately 10% (n= 1380) were aged over 65 years. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5 GRADE table: Efficacy of AZD1222 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: Two doses of AZD1222 vaccine
Comparison: Placebo/ active control
Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/ active control in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT(1;4)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-1
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial. No data were obtained on vaccination of pregnant or breastfeeding women, or persons who were immunocompromised.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.
[b] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Although persons with HIV were included in the trial, they were not included in the analyses. This was considered as constituting a limitation that leads to downgrading of the evidence.
[c] Underlying comorbidities included BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease or diabetes. Approximately 36% of the trial population had at least one comorbidity. This was considered as not constituting a limitation that would lead to downgrading of the evidence. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 6 GRADE table: Safety of AZD1222 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: One or two doses of AZD1222 vaccine
Comparison: Placebo/ active control
Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/ active control in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT(1;3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of AZD1222 vaccine is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.
[b] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events (i.e. less than about 1/800). These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination.
[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Although persons with HIV were included in the trial, they were not included in the analyses. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7 SAGE evidence-to-recommendation framework: AZD1222 vaccine use in adults

Question: Should AZD1222 vaccine be administered to adults to prevent COVID-19?
Population: Adults (18–64 years)
Intervention: Two doses of AZD1222 vaccine
Comparison(s): Active control/ placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are considered to be a critical tool to combat the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer-BioNTech and Moderna COVID-19 vaccine. (5;6)

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout the world (status 30 January 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
BENEFITS	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Using 07 December as data cut-off, primary efficacy analysis shows that AZD1222 vaccine is 63.1% (52.9%-68.6%) efficacious across the study population. In	The immunogenicity results from the phase 1/2 UK study, in 1077 healthy adults aged 18–55 years (2) and a phase

	Are the desirable anticipated effects large?	☐	☐	☒	☐	those 18-64 years of age, vaccine efficacy was 63.5 % (52.0-72.2). Vaccine efficacy in all participants varies by interval between first and second dose: <4 weeks interval: 66.56% (-221.8, 96.5) 4-8 weeks interval: 56.42% (39.9%-68.4%) 9-12 weeks interval: 70.48% (42.4%-84.9%) >12 weeks interval: 77.62% (52%-89.6%) Vaccine efficacy against COVID-19 occurring ≥ 22 Days after the first dose (and before the second dose or up to 12 weeks post first dose) was 71.42% (51.11, 84.08) in all participants.	2 cohort in older adults (≥56 years)(3) show the induction of binding and neutralising antibodies, with higher antibody titres after a second dose of vaccine.(2;3;7) The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose of AZD1222 nCoV-19 vaccine.(8)
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Data from over 12 021 participants demonstrate that AZD1222 vaccine was well tolerated across all populations. Overall, 86% of subjects in the vaccine group (Days 0-7 after any vaccination) experienced at least one solicited AE compared to 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one grade ≥3 local solicited adverse event (AE) and 8% at least one grade ≥3 systemic solicited event compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose compared with the first. The most frequently reported systemic solicited AEs in the vaccine dose 1 standard-dose group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced	The results from the phase 1/2 immunogenicity and safety trial suggest an acceptable safety profile in healthy adults aged 18–55 years (2) and a phase 2 study in older adults (≥56 years)(3)

			between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). There are no long-term safety data available yet and follow-up time remains limited.	
	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☒ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	Available scientific evidence on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), vary. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Available scientific evidence suggests that target population assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☒		*Uncertain* ☐	*Yes* ☐		*Varies* ☐	AZD1222 can be distributed and stored using existing cold chain infrastructure (at 2°-8° C),(9) and does not require ultra-cold chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world(10), its price is expected to be lower than for other COVID-19 vaccines using new and less widely available manufacturing platforms. Prices are also expected to be lower for AZD1222 compared to many other COVID-19 vaccines due to supplier commitments to forego profits.(11) Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (12). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (13).

	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of AZD1222 compared to other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower compared to some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g., hospitalizations averted; see Background Paper). The ability to use AZD1222 in existing cold chain infrastructure in all country settings may enable higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (12;14-20).
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (21), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of the AZD1222 vaccine are the same as those of many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (22).

ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒ | *Com-parison* ☐ | *Both* ☐ | *Neither* ☐ | *Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it.	190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general.
	Which option is acceptable to target group?	*Inter-vention* ☒ | *Com-parison* ☐ | *Both* ☐ | *Neither* ☐ | *Un-clear* ☐	COVID-19 vaccine acceptability in general varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (23). Polls have been launched, (periodically) assessing (non-product specific) vaccine acceptance in selected countries. These polls confirm overall vaccine acceptance, with variations across countries. (24;25)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☐	This vaccine is assumed to be easily implementable in settings, including low- and middle-income-countries, with existing vaccine logistics and delivery infrastructure. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Vaccination with AZD1222 vaccine is recommended in persons aged 18 and above. In light of the observation that two-dose efficacy and immunogenicity increase with a longer interdose interval, WHO recommends an interval of 8 to 12 weeks between the doses. If the second dose is inadvertently administered less than 4 weeks after the first, the dose does not need to be repeated. If administration of the second dose is inadvertently delayed beyond 12 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive two doses.				

Implementation considerations	
Monitoring, evaluation and research priorities	WHO recommends the following post-authorization monitoring activities and research. • Safety surveillance and monitoring: – serious adverse events, anaphylaxis and other serious allergic reactions, Bell`s palsy, transverse myelitis, cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death; – background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination. • Vaccine effectiveness: – vaccine effectiveness in older persons; – vaccine effectiveness in relation to time interval between the first and second dose; – vaccine effectiveness in relation to new virus variants; – vaccine effectiveness over time and whether protection can be prolonged by booster doses; – booster studies with heterologous vaccines; – studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; – assessment and reporting of breakthrough infections and virus sequence information; – head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays. • Subpopulations: – prospective studies on the safety of AZD1222 vaccine in pregnant and lactating women; – randomized controlled trials on efficacy and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries; – interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms; – stability of vaccine under alternative cold-chain distribution and storage conditions. • Virus variants – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – Modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants – Booster studies with updated vaccine formulations.

Annex 8:SAGE evidence-to-recommendation framework: AZD1222 vaccine use in older adults

Question: Should AZD1222 vaccine be administered to older adults to prevent COVID-19?
Population: Older adults (≥65 years)
Intervention: Two doses of AZD1222 vaccine
Comparison(s): Active control/ placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are considered to be a critical tool to combat the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer-BioNTech and Moderna COVID-19 vaccine. (5;6)

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout the world (status 30 January 2021). There has been collateral damage to other public health programmes. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Around 10% of the study population in the primary analysis (data cut-off 07 December 2020; trial COV001, COV002, COV003, COV005) were aged 65 years or older. Primary efficacy analysis using SDSD at any interval shows that two doses of AZD1222 vaccine is 51.9% (-60.9%-86.0%) efficacious in individuals aged 65 years and older against COVID-19 beginning 15 days after the second dose. A relatively small proportion of participants were aged 65 years or over and the number of cases of Covid-19 in this age group was too small to assess protection based on the efficacy data alone . There were no cases of Covid-19 hospitalisation, severe COVID-19 disease, or Covid-19 death in participants with ≥65 years of age who received the vaccine.	The immunogenicity results from the phase 1/2 UK study, in 1077 healthy adults aged 18–55 years (2) and a phase 2 cohort in older adults (≥56 years)(3) show the induction of binding and neutralising antibodies, with higher antibody titres after a second dose of vaccine.(2;3;7) The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose of AZD1222 nCoV-19 vaccine.(8)
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Data from over 12 021 trial participants of all age demonstrate that AZD1222 vaccine was well tolerated across all populations. Overall, 86% of subjects in the vaccine group (Days 0-7 after any vaccination) experienced at least one solicited AE compared to 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one grade ≥3 local solicited adverse event (AE) and 8% at least one grade ≥3 systemic solicited event compared with 6% and 3% in the control group, respectively. Solicited AEs were	

			milder and reported less frequently after the second dose compared with the first. Reactogenicity was generally milder and less frequent in older adults (≥65 years old) compared to younger adults (18-64 years). The most frequently reported systemic solicited AEs in the vaccine dose 1 standard-dose group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). There are no long-term safety data available yet and follow-up time remains limited.	
	Balance between benefits and harms	*Favours inter-vention* ☒ / *Favours com-parison* ☐ / *Favours both* ☐ / *Favours neither* ☐ / Unclear ☐	Evidence on efficacy data suggest some, though not significant benefit of the intervention, and short-term safety data suggest limited harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ / *Very low* ☐ / *Low* ☒ / *Mod-erate* ☐ / *High* ☐ Safety of the intervention	Please see the related GRADE tables.	

		No included studies ☐	*Very low* ☐	*Low* ☒	*Mod-erate* ☐	*High* ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☒	*Probably no important uncertainty or variability* ☐	*No important uncertainty or variability* ☐	*No known undesirable outcomes* ☐	The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the potential protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect. With more data on vaccine efficacy in older adults being generated, the uncertainty around the importance of the desirable effects of the intervention will be likely be reduced.	
RESOURCE USE	Are the resources required small?	*No* ☐		*Uncertain* ☐	*Yes* ☒		*Varies* ☐	AZD1222 can be distributed and stored using existing cold chain infrastructure (at 2°-8° C),(9) and does not require ultra-cold chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world(10), its price is expected to be lower than for other COVID-19	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion doses. This does not include all delivery costs in all

				vaccines using new and less widely available manufacturing platforms. Prices are also expected to be lower for AZD1222 compared to many other COVID-19 vaccines due to supplier commitments to forego profits.(11) Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (12). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (13).
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of AZD1222 compared to other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower compared to some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g., hospitalizations averted; see Background Paper). The ability to use AZD1222 in existing cold chain infrastructure in all country settings may enable higher population-level coverage.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (12;14-19).

						Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (21), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of AZD1222 vaccine is shared by many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (22).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒	*Com-parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination. But they may need to convince other partners or stakeholders to support COVID-19 immunization.	190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	COVID-19vaccine acceptability in general varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any	

		☒ ☐ ☐ ☐ ☐	COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (23). Polls have been launched, (periodically) assessing (non-product specific) vaccine acceptance in selected countries. These polls confirm overall vaccine acceptance, with variations across countries. (24;25)	
FEASIBILITY	Is the intervention feasible to implement?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☐ ☒ ☐	This vaccine is assumed to be easily implementable in settings, including low- and middle-income-countries, with existing vaccine logistics and delivery infrastructure. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Because a relatively small number of participants aged 65 years or over were recruited into the clinical trials, there were few cases of COVID-19 in either the vaccine or the control group in this age category, and thus the confidence interval on the efficacy estimate is very wide. More precise efficacy estimates for this age group are expected soon, from both ongoing trials and vaccine effectiveness studies in countries that are using this vaccine. Immune responses induced by the vaccine in older persons are well documented and similar to those in other age groups. This suggests it is likely that the vaccine will be found to be efficacious in older persons. The trial data indicate that the vaccine is safe for this age group. The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority group in the WHO SAGE Prioritization Roadmap. This prioritization is supported by vaccine impact modelling work , even for vaccine efficacy that is substantially below that observed among younger adults administered AZD1222. Taking the totality of available evidence into account, WHO recommends the vaccine for use in persons aged 65 years and older.			
Implementation considerations				
Monitoring, evaluation and research priorities	WHO recommends the following post-authorization monitoring activities and research. • Safety surveillance and monitoring: – serious adverse events, anaphylaxis and other serious allergic reactions, Bell`s palsy, transverse myelitis, cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death; – background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination. • Vaccine effectiveness: – vaccine effectiveness in older persons; – vaccine effectiveness in relation to time interval between the first and second dose;			

	– vaccine effectiveness in relation to new virus variants; – vaccine effectiveness over time and whether protection can be prolonged by booster doses; – booster studies with heterologous vaccines; – studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; – assessment and reporting of breakthrough infections and virus sequence information; – head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays. • Subpopulations: – prospective studies on the safety of AZD1222 vaccine in pregnant and lactating women; – randomized controlled trials on efficacy and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries; – interchangeability and "mix and match" studies within and across COVID-19 vaccine platforms; – stability of vaccine under alternative cold-chain distribution and storage conditions. • Virus variants – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – Modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants – Booster studies with updated vaccine formulations.

Question: Should AZD1222 vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[16] to prevent COVID-19?
Population: Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: Two doses of AZD1222 vaccine
Comparison(s): Active control/ placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are considered to be a critical tool to combat the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer-BioNTech and Moderna COVID-19 vaccine. (5;6)

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout the world (status	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website:

[16] Comorbidity within the phase III trial was defined as BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease or diabetes.

		☐	☐	☒	☐	30 January 2021). There has been collateral damage to other public health programmes. Individuals with certain comorbidities are particularly affected by COVID-19 and bear a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity (particularly a body mass index (BMI) >40). People with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes (26). Although the relative risk may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than for healthy older adults (>75 years).	https://covid19.who.int/table
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Approximately 36% of participants in the primary efficacy population, as well as of the overall study population, had at least one comorbidity at baseline. The most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%). Primary efficacy analysis (shows that AZD1222 vaccine is 61.3% efficacious (95%CI: 41.2-75.3%) against COVID-19 beginning 15 days after the second dose in adults with a comorbid condition at baseline.	The immunogenicity results from the phase 1/2 UK study, in 1077 healthy adults aged 18–55 years (2) and a phase 2 cohort in older adults (≥56 years)(3) show the induction of binding and neutralising antibodies, with higher antibody titres after a second dose of vaccine.(2;3;7) The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose of AZD1222 nCoV-19 vaccine.(8)
	Harms of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Overall, 86% of all subjects in the vaccine group (Days 0-7 after any vaccination), independent of comorbidity, experienced at least one solicited AE	

	Are the undesirable anticipated effects small?	☐ ☐ ☒ ☐	compared to 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one grade ≥3 local solicited adverse event (AE) and 8% at least one grade ≥3 systemic solicited event compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose compared with the first. The most frequently reported systemic solicited AEs in the vaccine dose 1 standard-dose group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). No data are currently available in immunocompromised subjects or in subjects taking immunosuppressants. Safety data is awaited in a subgroup of HIV positive subjects.	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ Unclear ☐	Efficacy data suggest benefit, and the short-term safety data suggest minimal harms. Further studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐ Safety of the intervention	Please see the related GRADE tables.	

		No included studies ☐ / *Very low* ☐ / *Low* ☒ / *Mod-erate* ☐ / *High* ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ / *Possibly important uncertainty or variability* ☒ / *Probably no important uncertainty or variability* ☐ / *No important uncertainty or variability* ☐ / *No known undesirable outcomes* ☐	There is possibly important uncertainty related to the target population weighing of desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals, related to COVID-19 vaccination. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☒ / *Yes* ☐ / *Varies* ☐	Available scientific evidence suggests that the target population probably attached more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☐ / *Un-certain* ☐ / *Yes* ☒ / *Varies* ☐	AZD1222 can be distributed and stored using existing cold chain infrastructure (at 2°-8° C),(9) and does not require ultra-cold chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world(10), its price is expected to be lower than for other COVID-19 vaccines using new and less widely available manufacturing platforms. Prices are also expected to be lower for AZD1222 compared to many other COVID-19 vaccines due to supplier commitments to forego profits.(11) Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion vaccine doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (12). The World Bank has approved a financing window of up to US$12 billion

						programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	to support low- and middle-income countries in purchasing and distributing vaccine (13).
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of AZD1222 compared to other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower compared to some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g., hospitalizations averted; see Background Paper). The ability to use AZD1222 in existing cold chain infrastructure in all country settings may enable higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (12;14-19)
EQ		*Increa-sed*	*Un-certain*	*Reduced*	*Varies*	Equity and ethical considerations are critical. SAGE has produced a Values Framework (21), which offers	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as

	What would be the impact on health inequities?	☐ ☐ ☒ ☐	guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of AZD1222 vaccine is shared by many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution.	high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (22).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination. But they may need to convince other partners or stakeholders to support COVID-19 immunization.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	COVID-19 vaccine acceptability in general varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (23). Polls have been launched, (periodically) assessing (non-product specific) vaccine acceptance in selected countries. These polls confirm overall vaccine acceptance, with variations across countries. (24;25)	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	This vaccine is assumed to be easily implementable in settings, including low- and middle-income-countries, with existing vaccine logistics and delivery infrastructure. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	**Persons with comorbidities** Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The Phase 3 clinical trial demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in the Phase 3 clinical trials included obesity; cardiovascular disease; respiratory disease, and diabetes. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19. **Immunocompromised persons** Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons including those receiving immunosuppressant therapy. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus vaccine, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment. **Pregnant women** Pregnant women are at higher risk of severe COVID-19 compared to women of child-bearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. The available data on AZD1222 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, it should be noted that the AZD1222 is non-replicating vaccine. Animal developmental and reproductive toxicity (DART) studies are ongoing. Based upon results from the preliminary findings, no harms are expected on the development of the fetus. Further studies are planned in pregnant women in the coming months including a pregnancy sub-study and a pregnancy registry. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, pregnant women should only receive AZD 1222 if the benefit of vaccination to the pregnant woman outweighs the potential vaccine risks, such as pregnant women who are health workers at high risk of exposure and pregnant women with comorbidities that already place them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy because of vaccination. **Lactating women** Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. It is unknown whether AZD1222 is excreted in human milk. As the AZD1222 vaccine is non-replicating vaccine, it is unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g. health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination. **Persons living with HIV** Persons living with HIV may be at higher risk of severe COVID-19. Persons living with HIV were not included in the primary analyses of the Phase 3 trials and safety data is awaited in a subgroup of HIV positive subjects. Data on administration of the vaccine are currently insufficient to allow

	assessment of vaccine efficacy or safety for persons living with HIV. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is a non-replicating vaccine, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration. **Persons with autoimmune conditions** No data are currently available on the safety and efficacy of AZD1222 in persons with autoimmune conditions. Persons with autoimmune conditions who have no contraindications to vaccination may be vaccinated.
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and cold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In the countries where various immunization stakeholders have a crucial role in the vaccine distribution, information and open discussion will be required before the vaccine is deployed.
Monitoring, evaluation and research priorities	WHO recommends the following post-authorization monitoring activities and research. • Safety surveillance and monitoring: – serious adverse events, anaphylaxis and other serious allergic reactions, Bell`s palsy, transverse myelitis, cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death; – background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination. • Vaccine effectiveness: – vaccine effectiveness in older persons; – vaccine effectiveness in relation to time interval between the first and second dose; – vaccine effectiveness in relation to new virus variants; – vaccine effectiveness over time and whether protection can be prolonged by booster doses; – booster studies with heterologous vaccines; – studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; – assessment and reporting of breakthrough infections and virus sequence information; – head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays. • Subpopulations: – prospective studies on the safety of AZD1222 vaccine in pregnant and lactating women; – randomized controlled trials on efficacy and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries;

	– interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms; – stability of vaccine under alternative cold-chain distribution and storage conditions. • Virus variants – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – Modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants – Booster studies with updated vaccine formulations.

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