This background document was developed to inform the initial recommendation-making process. It is not updated on a regular basis. The latest Grade and ETR tables can be obtained here:
https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-GRADE-ETR-2021.1

Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca

Background document to the WHO Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca

1 March 2021

World Health Organization

Contents

Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 8 February 2021 extraordinary meeting, which resulted in the issuance of the 10 February 2021 WHO Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca. Both recommendations and background document are available on the SAGE Covid-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

Context

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, and so use of simian adenoviruses might be preferable. COVID-19 Vaccine AstraZeneca, also known as AZD1222 or ChAdOx1-S (recombinant), was developed by Oxford University, United Kingdom, and AstraZeneca, 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 vector encoding the S glycoprotein of SARS-CoV-2 (ChAdOx1-S (recombinant). The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric prefusion conformation; the coding sequence has not been modified, in order to stabilize the expressed S-protein in the prefusion 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 leader sequence uses a modified human cytomegalovirus promoter and a bovine growth hormone polyadenylation sequence.

The following information is derived from the product information approved by the European Medicine Agency`s Committee for Medicinal Products for Human Use (CHMP)(1).

Composition

One dose (0.5ml) contains 5 x 10^{10} ChAdOx1-S (recombinant) 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 injection. None of the excipients are of animal or human origin. The excipients are well established for pharmaceutical products.

Stability and Shelf-life

A shelf-life of 6 months is proposed. Chemical and physical in-use stability from the time of vial opening (first needle puncture) to administration is up to 48 hours in a refrigerator (2–8 ºC). Within this period, the product may be kept and used at temperatures up to 30 ºC for a single period of up to 6 hours, after which it must be discarded. It should not be returned to the refrigerator.

Drug product description

The product is a colourless to slightly opalescent solution provided in a multidose vial with an elastomeric stopper and aluminium overseal. The drug product vials are packaged in cartons of 10 vials.

Container

Different presentations of the multidose vial will be available in different regions. For example:

- In the European Union, the product will be available in 4-ml (8-dose) and 5-ml (10-dose) vials.
- 5 ml (10-dose) vials will be made available through COVAX.

- Covishield, produced by the Serum Institute of India (SII), is expected to be available in vials containing 1 dose (0.5 ml), 2 doses (1.0 ml), 5 doses (2.5 ml), 10 doses (5.0 ml) or 20 doses (10 ml).

Pharmacokinetics

Two biodistribution studies have been performed, which suggested that, after injection, the virus does not replicate or persist, and is not distributed in the body beyond the injection site in a way that would be clinically significant.

Developmental and reproductive toxicity

Animal developmental and reproductive toxicity (DART) studies are ongoing. A dose-range study and a GLP embryo-foetal development study were completed. In top-line results from the latter study, no test item-related effects were seen for dams in-life, including at the injection site, for female reproduction, foetal or pup survival or pup physical development, and there were no abnormal gross pathology findings in pups before or after weaning or in dams in either phase. There were no test item-related foetal external, visceral or skeletal findings. The audited report is due later in 2021.

Lactation

There have so far been no studies of the safety of this vaccine in women who are breastfeeding. Studies are planned to address this issue.

Preclinical studies

The following information is derived from scientific publications.

The efficacy of AZD1222 vaccine was assessed in rhesus macaque monkeys (2). Six animals per group were vaccinated intramuscularly with 2.5×10^{10} ChAdOx1-S (recombinant) virus particles each, using either a prime-only regimen (28 days before challenge) or a prime–boost regimen (56 and 28 days before challenge). 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 vaccination (two-tailed signed-rank Wilcoxon test). Endpoint IgG titres of 400–6400 (prime) and 400–19 200 (prime–boost) were measured on the day of challenge. Virus-specific neutralizing antibodies were also significantly increased after the second vaccination (two-tailed signed-rank Wilcoxon test) and were detectable in all vaccinated animals before challenge (titres 5–40 (prime) and 10–160 (prime–boost)). No virus-specific neutralizing antibodies were detected in control animals. On the day of challenge, IgM antibodies were present in the serum of all six prime–boost animals and two of the six prime-only animals. SARS-CoV-2 spike-specific T-cell responses were detected on the day of challenge by gamma interferon (IFNγ) ELISpot assay, after 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, $P = 0.3723$). Vaccination with ChAdOx1-S (recombinant) has been shown to induce 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 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, $r^2 = 0.6493$ $P = 0.0529$).

After challenge, the animals were evaluated for the protection offered by the vaccine and the potential for vaccine-associated enhanced respiratory disease (VAERD) (2). The clinical disease score in vaccinated monkeys was lower than that in the controls, and the vaccine prevented damage to the lungs. The prime–boost regimen induced humoral immune responses. Viral loads in the lungs were lower than in controls, but there was no reduction in viral shedding from the nose with either the prime-only or the prime–boost regimen. This suggests that AZD1222 may not prevent infection or transmission of SARS-CoV-2, but may reduce illness. The immune responses were not skewed towards a Th2-type and there was no suggestion of enhanced disease following vaccination. While a single dose induced antigen-specific antibody and T-cell responses, a booster immunization enhanced antibody responses, with a significant increase in SARS-CoV-2 neutralizing titres (3).

Clinical studies

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

- COV001, a phase 1/2 trial conducted in the United Kingdom;
- COV002, a phase 2/3 trial conducted in the United Kingdom:
- 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 under way in other countries, including India, Japan, Kenya, Russian Federation and South Africa. In addition, a large phase 3 trial involving about 30 000 participants is taking place in Argentina, Chile, Colombia, Peru and the USA; interim results from this trial are expected shortly.

The primary analysis of vaccine efficacy is used here as the main source of data. These data were made available by AstraZeneca for review, and permission has been given for these data to be made public in this background document.

Immunogenicity studies in humans

COV001 study (4–6)

A total of 1077 participants were enrolled in this study, of whom 543 were randomized to receive AZD1222, while the rest received meningococcal group A, C, W and Y conjugate vaccine (MenACWY) as control. Subsequently, some AZD1222 recipients received boosters at different doses and dose intervals. Binding antibody responses, as measured by enzyme-linked immunosorbent assay (ELISA), were consistently detected after one dose and were substantially boosted following a second dose, correlating with neutralizing antibody titres. The latter were measured using several methods and were detectable in all subjects after two doses, 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 IFNγ and tumour necrosing factor (TNF) alpha on days 7 and 14 (rather than a Th2-bias (IL-4 and IL-13)).

A standard dose (SD) booster of 5×10^{10} viral particles (vp) administered 56 days after the priming dose induced a rise in polyfunctional antibody concentrations (7). These were higher than following low dose (LD) boosters of 2.2×10^{10} or 2.5×10^{10} vp, 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 neutralizing antibody responses were detectable, their presence was not associated with reduced antibody or T cell anti-SARS CoV2 responses to booster vaccine doses.

Anti-spike neutralizing antibody titres, as well as Fc-mediated functional antibody responses, including antibody-dependent neutrophil/monocyte phagocytosis, complement activation and natural killer cell activation, were substantially increased by a booster dose of vaccine. A full SD booster induced stronger antibody responses than an LD boost, although the magnitude of T-cell responses did not increase with either dose. The booster dose of AZD1222 was found to be safe and better tolerated than the priming doses.

COV002 study (7)

In the first part of this phase 2/3 trial, 560 subjects in three different age groups (18–55, 56–69 and ≥70 years) were enrolled and received either one (older two groups) or two doses of AZD1222 or MenACWY (control) vaccine, 28 days apart. Two dose regimens were used (LD and SD).

The median anti-spike SARS CoV-2 IgG responses 28 days after the booster dose were similar across the three age cohorts, as were the neutralizing antibody titres. T-cell responses peaked on day 14 after a single SD and did not increase significantly after the booster vaccination.

The antibody response tended to be slightly lower with the LD regimen compared with the SD regimen on day 56.

The rate of seroconversion (a 4-fold or greater increase over baseline) to S-binding antibodies was over 98% 28 days after the first dose and over 99% 28 days after the second dose for participants who were seronegative at baseline. The rate of seroconversion, as measured in a live neutralization assay, was over 80% 28 days after the first dose and over 99% 28 days after the second dose for participants who were seronegative at baseline.

AZD1222 appeared to be better tolerated in older adults than in younger adults and had similar immunogenicity across all age groups after a booster dose.

In the COV002 study, some participants assigned to receive SD prime 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 prime and booster doses (SDSD), the dose intervals varied, 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 those given the standard priming dose with a longer dose interval.

Efficacy

The efficacy analysis reported reflects data collected up to 7 December 2020 in the four studies, and includes patients who received two standard doses (SDSD) with any interval between doses (ranging from 3 to 23 weeks (21 to 159 days)).

COV001 (United Kingdom, phase 1/2). This study in adults aged 18–55 years was designed to evaluate various dosing regimens, and used a single dose or a 2-dose regimen of AZD1222 or MenACWY (control), different dose levels (SD and LD), and various dosing schedules.

COV002 (United Kingdom, phase 2/3). This study enrolled participants in 19 study sites and targeted individuals working in professions with a high possible exposure to SARS-CoV-2, such as those working in health and social care settings. The study began by enrolling participants aged 18–55 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 4–12 weeks and about 20% had an interval in excess of this.

COV003 (Brazil, phase 3). This study enrolled participants at high risk of exposure to the virus, including health care workers, in six sites across the country. Recruitment of participants in Brazil began a little later than the COV002 study in the United Kingdom, and they were offered two doses of the vaccine up to 12 weeks apart (target 4 weeks). Participants received either two doses of AZD1222 or a first dose of MenACWY and a second dose of saline placebo. For less than 2% of participants, the interval between doses was more than 12 weeks.

COV005 (South Africa, phase 1/2). This study enrolled adults living with or without HIV at seven sites in the country. The study started at approximately the same time as the study in Brazil; participants received two doses of AZD1222 vaccine or saline placebo at a dose interval between less than 4 weeks and 12 weeks. The dose interval was never more than 12 weeks.

Women who were pregnant or breastfeeding were excluded from all studies.

Baseline demographics were well balanced across the vaccine and control groups. In the pooled analysis of all four studies, among the participants who received two standard doses (SDSD) of the vaccine with any interval between doses (data cut-off 7 December 2020): 90.2% of participants were 18–64 years old and 9.8% were aged 65 or older; 54.4% of subjects were female; 71.8% were white, 11.8% were black and 3.4% were Asian. In total, 2592 participants (36.0%) had at least one pre-existing comorbidity (defined as a body mass index (BMI) ≥30 kg/m^2, 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 dose.

Efficacy against COVID-19

The primary endpoint was specified as efficacy against symptomatic COVID-19 15 days or more after the second dose among participants who were seronegative at trial entry. A total of 14 380 participants were eligible for inclusion in the efficacy analysis (43% in the United Kingdom, 47% in Brazil, 10% in South Africa). There were 271 COVID-19 cases with onset 15 days or more after dose 2, with 74 cases in the vaccinated group and 197 in the control group. The estimate of vaccine efficacy (VE) was 63.09% (95% confidence interval (CI) 51.81–71.73%).

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 group and 8 in the control group (VE 51.91%; 95% CI –59.98% to 85.54%).

Exploratory analyses were conducted of vaccine efficacy 15 days or more 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, for 22% 9–12 weeks and for 16% more than 12 weeks. The estimates of VE increased significantly in these 3 groups, being 56%, 70% and 78%, respectively.

During the 21 days after the first dose, there was no difference between the vaccine and control groups in COVID-19 incidence. 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 hospitalization (WHO clinical progression scale ≥4)

In the total trial population, there were 24 patients who needed to be hospitalised for COVID-19, 2 in the vaccine group and 22 in the control group. During the period from 22 days after the first dose, there were no hospitalized cases in the vaccinated group and 14 in the control group. For the period from 15 or more days after dose 2, there were, respectively, 0 and 8 hospitalized cases.

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

In the total population, there were only three 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 after a second dose was given (VE 71.42%). The primary trial endpoint was efficacy measured from 15 days after the second vaccine dose until data cut-off, which was, on average, about 2 months (mean 58 days; median 66 days) after the second dose. The vaccine continued to be efficacious during this period (VE 63.09%). Exploratory analyses indicated that efficacy following the second dose increased with increasing interval 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 COVID-19 hospitalizations, severe COVID-19 disease, or COVID-19 deaths in participants ≥65 years of age who received AZD1222.

A summary of the main findings is presented in Table 1.

Table 1. Vaccine efficacy against virologically confirmed COVID-19 occurring 15 days or more after the second dose

Subgroup	Participants with events		VE (%)	95%CI (%)	P value
	AZD1222 No. (%)	Control No. (%)			
SDSD, any dose interval					
Overall	74/7201 (1.03)	197/7179 (2.74)	63.09	(51.81, 71.73)	<0.001
Age group					
≥ 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					
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
Sex					
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					
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					
4–8 weeks	54/4796 (1.13)	117/4662 (2.51)	56.42	(39.86, 68.43)	<0.001
9–12 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

The safety analysis reported in this document reflects data obtained up to 4 November 2020.