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

DRAFT

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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