Clinical Study Report Addendum Synopsis	
Drug Substance	AZD1222
Study Code	D8111C00002
Edition Number	1
Date	29 March 2022
NCT Number	NCT04568031

A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19

Study Dates:
First subject enrolled: 23 August 2020
Last subject last visit: 22 November 2021
The analyses presented in this report are based on a database lock date of 17 January 2022.

Phase of Development:
Phase I/II

Sponsor's Responsible Medical Officer:
PPD
AstraZeneca
BioPharmaceuticals R&D
Vaccines & Immune Therapies
PPD
Cambridge
CB2 8PA, United Kingdom

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

This study was performed in 5 clinical study centers in Japan.

Publications

Asano M, Okada H, Itoh Y, Hirata H, Ishikawa K, Yoshida E, et al. Immunogenicity and safety of AZD1222 (ChAdOx1 nCoV-19) against SARS-CoV-2 in Japan: a double-blind, randomized controlled phase 1/2 trial. Int J Infect Dis. 2022;114:165-74.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Immunogenicity	• To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to Spike antigen of AZD1222 (MSD serology assay) at Day 57.
Primary	Safety	• To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.	(a) Occurrence of solicited local reactogenicity signs and symptoms for 7 days following throughout vaccination. (b) Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following throughout vaccination. (c) Occurrence of AEs, SAEs and AESIs for 28 days following throughout vaccination. (d) Change from baseline for safety laboratory measures.
Secondary	Immunogenicity	• To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to RBD antigen of AZD1222 (MSD serology assay) at Day 57.
Secondary	Immunogenicity	• To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay).	• Geometric mean titers and GMFR of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) at each time point up to Day 365.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Immunogenicity	• To assess the function of nAb against SARS-CoV-2 Spike protein.	• Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 nAb (wild-type assay or pseudoneutralization assay) at Day 57. • Geometric mean titers and GMFR of immunogenicity to Spike antigen of AZD1222 as measured by SARS-CoV-2 nAb at each time point up to Day 365.
Secondary	Safety	• To assess the safety of the candidate vaccine AZD1222.	• Occurrence of SAEs and AESIs throughout the study duration up to Day 365.
Exploratory	Descriptive efficacy	• To describe occurrence of symptomatic coronavirus disease 2019 (COVID-19) in recipients of AZD1222 and placebo.	• Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
Exploratory	Descriptive efficacy	• To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.	(a) Hospital admissions associated with COVID-19. (b) Intensive care unit admissions associated with COVID-19. (c) Deaths associated with COVID-19. (d) Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay).

Study days for vaccinations were Day 1 and Day 29.

AE, adverse events; AESI, adverse events of special interest; COVID-19, coronavirus disease 2019; GMFR, geometric mean fold rise; IM, intramuscular; MSD, Meso Scale Discovery; nAb, neutralizing antibodies; RBD, receptor-binding domain; RT-PCR, reverse transcriptase-polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

Study design

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 52 week Phase I/II study. In this study, 256 eligible, healthy, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-naïve participants were randomized in a 3:1 ratio to receive 2 intramuscular (IM) doses of either AZD1222 with 5×10^{10} vp (viral particles; nominal) or placebo administered 4 weeks apart.

The study had 2 cohorts with different age populations. Cohort C included healthy, SARS-CoV-2-naïve participants aged 18 to 55 years. Cohort D included healthy, SARS-CoV-2-naïve elderly participants aged ≥ 56 years. In Cohort D, the elderly population was further divided into 2 different age subgroups; aged 56 to 69 years (Subcohort D1) and aged ≥ 70 years (Subcohort D2). One hundred and twenty-eight participants in each cohort were randomized in a 3:1 ratio to receive either AZD1222 or placebo.

An independent Neurological Adverse Event of Special Interest (AESI) Expert Committee was available to review and provide advice to the Sponsor about the diagnosis and causality assessment of selected AESIs.

This clinical study report (CSR) Addendum presents the results for the final analysis for this study, characterizing immunogenicity and safety profiles of AZD1222 in participants aged 18 years or older, including endpoints up to Day 365 in all participants (see Statistical methods below).

Target population and sample size

Regarding Cohort C, 128 participants were randomized in a 3:1 ratio to receive either AZD1222 or placebo. Regarding Cohort D, in a similar way, 128 participants were randomized in a 3:1 ratio to receive either AZD1222 or placebo, but participants were stratified at randomization by age group (ie, Subcohorts D1 versus D2). At least 30% of enrollment positions in Cohort D were secured for participants of age ≥ 70 years.

These sample sizes (96 for AZD1222 versus 32 for placebo) were determined mainly for safety evaluation and based on feasibility. With the sample size of 96 participants in the AZD1222 treatment arm in each cohort, at least one participant with an adverse event (AE) of incidence rate of 2.5% can be detected with probability of about 90%. The placebo arm was required for securing the objectivity of the safety evaluation of the AZD1222 arm and also as a control for evaluating immunogenicity as stated below. For these purposes, the minimum sample size was given to the placebo arm (one third of the AZD1222 arm).

It was difficult to calculate an accurate sample size necessary for comparing the proportion of participants who have a seroresponse to SARS-CoV-2 Spike (S) protein between the AZD1222 and placebo arms because of insufficient information on immunogenicity in both arms at the time of study design. However, under a conservative assumption about seroresponse rates of 10% assumed on placebo and over 50% on AZD1222, it was expected that the sample size stated above (96 for AZD1222 versus 32 for placebo) would provide 99% power for showing seroresponse superiority of the AZD1222 treatment compared with placebo based on Fisher's exact test at 2-sided 5% alpha.

Investigational product and comparator: dosage, mode of administration, and batch numbers

Participants received either AZD1222 (previously known as ChAdOx1 nCoV-19) or placebo. AZD1222 with 5×10^{10} vp (nominal) or placebo were administered IM on Day 1 and Day 29.

One batch of AZD1222 (A03369) was used in this study. Placebo was 0.9% weight/volume saline sourced locally, and batch numbers are therefore not applicable.

Duration of treatment

Participants received 2 doses of study treatment: one on Day 1 and one on Day 29.

Statistical methods

The study was paused to allow a safety review following the occurrence of a serious adverse event (SAE) of transverse myelitis in a University of Oxford-sponsored trial of AZD1222 in the United Kingdom (Study COV002 [NCT04400838]). By that time (07 September 2020), 99 participants had been vaccinated. In order not to delay the local (Japan) vaccine assessment, the analysis strategy was updated, and was performed in the following 3 steps:

- A primary analysis including immunogenicity data up to Day 57 from participants enrolled before the study interruption and safety data gathered in all participants up to Day 57.
- An additional analysis including immunogenicity data in all participants up to Day 57.
- A final analysis including endpoints up to Day 365 in all participants (reported in this CSR Addendum).

For the immunogenicity endpoints, only the analyses of geometric mean titers (GMT) and geometric mean fold rise (GMFR) of immunogenicity against S and receptor-binding domain (RBD) antigens of AZD1222 and to S antigen of AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (nAb) at each time point up to Day 365 were conducted for the final analysis.

Geometric mean titers and GMFRs were calculated for AZD1222 and placebo and were summarized for the total vaccinated analysis set (TVS) and for the fully vaccinated analysis set (FVS) for immunogenicity at each scheduled visit, for the following titer measurements:

- Antibodies against S and RBD antigens of AZD1222 based on Meso Scale Discovery (MSD) serology assay.
- Neutralizing antibodies (pseudoneutralization) to SARS-CoV-2.

Descriptive statistics for GMTs and GMFRs included number of participants, geometric mean, 95% confidence interval, minimum, and maximum and were presented by Cohorts C and D, and Subcohorts D1 and D2 separately.

For the safety endpoints, no formal statistical analyses were performed. For the final analysis, only descriptive summaries of unsolicited AEs (including all unsolicited AEs in the 28-day period after each dose of study intervention and unsolicited AEs that started post 28 days of each dose of study intervention and were observed as SAEs or identified as AESIs), SAEs, AESIs, and vital signs up to Day 365 were presented by cohort, and physical examination data were included in participant listings.

For the exploratory efficacy endpoints:

- The incidence of the first virologically confirmed (reverse transcriptase-polymerase chain reaction [RT-PCR] positive) symptomatic cases of coronavirus disease 2019 (COVID-19) was to be summarized for the TVS, and the incidence of COVID-19 occurring ≥ 15 days post second dose of study intervention was to be summarized for the FVS for efficacy and presented for the AZD1222 and placebo groups by cohort.

  Kaplan-Meier curves were to be presented for AZD1222 and placebo in the TVS and FVS for efficacy, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR positive symptomatic COVID-19 post first dose of study intervention or occurring ≥ 15 days post second dose of study intervention, respectively.
- Assessments of the incidence of hospital admissions, intensive care unit (ICU) admissions and deaths associated with COVID-19, and the proportions of participants who had seroresponse to the non-Spike (nucleocapsid) SARS-CoV-2 antigens based on MSD serology assay were to be described for the TVS and the FVS for efficacy by treatment.

Data handling for participants inoculated with non-study COVID-19 vaccine

For participants who were inoculated with non-study COVID-19 vaccine, immunogenicity and exploratory efficacy data from the time of the non-study COVID-19 vaccination were not included in the analyses, ie, any immunogenicity data collected after the date of non-study COVID-19 vaccination were removed from the summaries; however, these data were included in participant listings.

For participants who were inoculated with non-study COVID-19 vaccine and did not meet the criteria for virologically confirmed (RT-PCR) symptomatic cases of COVID-19 up to the time of COVID-19 vaccine inoculation, time to event was censored based on the date of the non-study COVID-19 vaccination.

The analysis of AEs was presented with all data, including safety data of participants who were inoculated with a non-study COVID-19 vaccine. The same analysis was provided for the following:

- After removing all safety data that started post non-study COVID-19 vaccination, and
- Only safety data that started post non-study COVID-19 vaccination for participants who were inoculated with a non-study COVID-19 vaccine.

Study population

A total of 415 participants were screened, of whom 128 were randomized in Cohort C and 128 were randomized in Cohort D. Overall, the majority of participants received both doses of study intervention (AZD1222: 176 participants [91.7%]; placebo: 61 participants [95.3%]). Some participants who had received the first dose of study intervention withdrew consent to receive the second dose after the study was paused to allow a safety review following the occurrence of an SAE of transverse myelitis in a University of Oxford-sponsored trial of AZD1222 in the United Kingdom (Study COV002 [NCT04400838]). No participant had discontinued from the study before 28 days post second dose, ie, through Day 57. By Day 365, 7 participants (3.6%) in the AZD1222 group had discontinued from the study (withdrawal by participant: n = 4; physician decision: n = 2; lost to follow-up: n = 1), as had one participant (1.6%) in the placebo group (withdrawal by participant).

In Cohort C, 25.8% of participants were female, all were Asian, and the mean (standard deviation [SD]) age was 45.7 (7.81) years. In Cohort D, all participants were Asian; the proportion of female participants (42.2%) was higher than in Cohort C. In Subcohort D1 the mean (SD) age was 61.3 (3.71) years, with 24.4% of participants ≥ 65 years of age, and in Subcohort D2 the mean (SD) age was 73.2 (3.45) years. The proportion of participants in both cohorts with body mass index ≥ 30 kg/m^2 was low (Cohort C: 6.3%; Cohort D: 2.3%).

The numbers of important protocol deviations in Cohorts C and D were low and were not considered to have had an impact on the conduct or quality of the study.

The characteristics of the participants who received the study intervention were consistent with the intended target population and were well-balanced between the AZD1222 and placebo arms of Cohorts C and D, including Subcohorts D1 and D2.

Due to the study pause (see Statistical methods above for details), in order not to delay the local (Japan) vaccine assessment, the analysis for this study was performed in the following 3 steps:

- A primary analysis including immunogenicity data up to Day 57 from participants enrolled before the study interruption (FVS for immunogenicity: AZD1222: N = 61, placebo: N = 20; TVS: AZD1222: N = 75, placebo: N = 24) and safety data gathered in all participants up to Day 57 (TVS: AZD1222: N = 192, placebo: N = 64), reported in the CSR for the primary analysis dated 25 February 2021.
- An additional analysis including immunogenicity data in all participants up to Day 57 (FVS for immunogenicity: AZD1222: N = 174, placebo: N = 60; TVS: AZD1222: N = 192, placebo: N = 64), reported in the CSR Addendum for the additional analysis dated 19 March 2021.

- A final analysis including endpoints up to Day 365 in all participants, reported in this CSR Addendum for the final analysis (FVS for immunogenicity: AZD1222: N = 174, placebo: N = 60; TVS: AZD1222: N = 192, placebo: N = 64).

Summary of efficacy results (exploratory)

Exploratory efficacy analyses were performed on the FVS for efficacy, with supportive analyses performed on the TVS.

Two participants tested positive for COVID-19 during the study, both in the Cohort C AZD1222 group: one asymptomatic participant who had taken a PCR test for travel and one symptomatic participant who had taken an antigen test.

There were no deaths, hospital admissions, or ICU admissions associated with COVID-19 during the study.

No participant in the placebo group had a seroresponse to SARS-CoV-2 nucleocapsid antigen at any time during the study. Although breakthrough infections were reported in a few participants in the AZD1222 group at specific time points during the study (Day 57: 2 participants; Day 183: 2 participants, Day 365: 9 participants), these results should be interpreted with caution considering the exploratory nature of these analyses, the low numbers of participants with seroresponse to SARS-CoV-2 nucleocapsid antigen in the AZD1222 group, and the small sample size (n = 7) of participants in the pooled placebo group who had not received non-study COVID-19 vaccines and were, therefore, included in the analysis at Day 365. Indeed, censored at non-study COVID-19 vaccination, the median (range) follow-up time in the AZD1222 group was 355.5 (183 to 383) days compared with 268.0 (140 to 365) days in the placebo group, confounding the ability to compare exploratory efficacy in these groups.

Summary of immunogenicity results

Immunogenicity analyses were performed on the FVS for immunogenicity, with supportive analyses performed on the TVS.

In the AZD1222 group, antibody titers for the S- and RBD-binding antibodies and for the nAb (pseudoneutralization) to SARS-CoV-2 increased substantially after the first dose of study intervention, increasing further after the second dose, which suggests that AZD1222 elicits strong early humoral immune responses against SARS-CoV-2 (S, RBD, and nAb [pseudoneutralization]) in the adult Japanese population. Data show a slightly decreasing trend in titers with increasing age, although a large variability was observed in the individual titers, with overlap in confidence intervals between cohorts.

By Day 183, mean antibody titers in all cohorts were below Day 29 pre-dose levels due to expected waning of humoral immunogenicity. By Day 365, mean titers of S- and

RBD-binding antibodies remained above Baseline and Day 15 levels; however, a large proportion of participants had no measurable nAb (pseudoneutralization) at this time point.

In the pooled (Cohorts C + D) placebo group, there were no changes from baseline for the antibody titers through Day 183. A numerical increase over baseline GMT was observed at Day 365, possibly due to under-reporting of non-study COVID-19 vaccines received.

No notable patterns or trends were observed in the subgroup analysis by body mass index (BMI). In the AZD1222 group, numerically higher GMT values were observed at Day 57 in female participants compared with male participants for S, RBD, and nAb; no notable difference was evident at Day 365. However, given the exploratory nature of these subgroup analyses, and the small sample sizes (especially for participants with BMI ≥ 30 kg/m^2), the results should be interpreted with caution.

Summary of safety results

Safety analyses were performed on the TVS unless otherwise stated; data from all participants (N = 256) up to Day 365 were included.

AZD1222 administered in 2 IM injections was well-tolerated and had an acceptable safety profile in Japanese participants, including older participants and those with controlled underlying diseases.

- The summaries of unsolicited AEs in the final analysis included data for all unsolicited AEs up to Day 57 and only those AEs that were observed as SAEs or identified as AESIs between Day 58 and Day 365. In this report, the term *unsolicited AEs* refers collectively to all unsolicited AEs up to Day 57 and only SAEs and AESIs from Day 58 up to Day 365.
  - A small number of SAEs and AESIs were reported between Day 58 and Day 365 in addition to the unsolicited AEs collected up to Day 57. In total, excluding data post non-study COVID-19 vaccination, 5 participants experienced a total of 8 SAEs during the study: in the AZD1222 group, this included Grade 2 colon adenoma in one participant in Cohort D1, Grade 2 pneumonia (2 events) and Grade 2 cerebral hemorrhage in one participant in Cohort D2, and Grade 2 bile duct stone and Grade 4 small intestine carcinoma in one participant in Cohort D2; in the placebo group, this included Grade 3 sinus node dysfunction in one participant in Cohort C and Grade 3 cervical dysplasia in one participant in Cohort D1 (Food and Drug Administration severity grading). None of these events were assessed as related to study intervention by the Investigator. No participant had AESIs during the study excluding data post non-study COVID-19 vaccination.
  - Post non-study COVID-19 vaccination, one participant in the placebo group in Cohort C experienced a Grade 2 SAE of anaphylactic reaction that was assessed as

related to the non-study COVID-19 vaccine that the participant received. This event was an AESI.

- Overall, excluding data post non-study COVID-19 vaccination, 26.0% of participants in the AZD1222 group and 20.3% of participants in the placebo group experienced at least one unsolicited AE during the study.
  - Unsolicited AEs were reported less frequently after the second dose of study intervention compared with after the first dose in both the AZD1222 group (11.4% and 19.8% of participants, respectively) and the placebo group (6.6% and 15.6%, respectively); this was consistent across cohorts. Additionally, fewer unsolicited AEs of ≥ Grade 3 severity were reported after the second dose of study intervention compared with after the first dose in both the AZD1222 and placebo groups.
  - There were no notable imbalances in the incidence or type of preferred terms (PTs) not commonly associated with vaccination between the AZD1222 and placebo groups. The most commonly reported unsolicited AEs after any vaccination were tenderness (5.7%) and injection site pain (4.2%) in the AZD1222 group and fatigue (4.7%) in the placebo group.
  - In the AZD1222 group, unsolicited AEs were reported in fewer participants in Cohort D compared with participants in Cohort C; the differences were primarily driven by PTs commonly associated with vaccination.
  - The majority of participants who experienced unsolicited AEs had AEs that were of mild (Grade 1) or moderate (Grade 2) severity after any vaccination, with severe (Grade 3) AEs reported in 6 participants (3.1%) and 3 participants (4.7%), respectively, in the AZD1222 and placebo groups, and a potentially life-threatening (Grade 4) AE (PT small intestine carcinoma; unrelated to study intervention) reported in one participant (0.5%) in the AZD1222 group. No fatal (Grade 5) AEs were reported.
  - Overall, unsolicited AEs assessed as related to study intervention by the Investigator were reported in 27 participants (14.1%) in the AZD1222 group and 5 participants (7.8%) in the placebo group. Unsolicited AEs of ≥ Grade 3 severity that were considered related to study intervention were reported in 4 participants (2.1%) in the AZD1222 group and none in the placebo group.
  - No participant died during the study.
  - No clinically relevant notable difference was observed between the AZD1222 and placebo groups in vital signs assessments or physical examinations.
  - Results of subgroup analyses by BMI group (< 30 kg/m^2, ≥ 30 kg/m^2) and gender (female, male) were generally consistent with those of the overall population, with no notable patterns or trends observed. However, given the exploratory nature of these subgroup analyses and the small sample sizes (especially for participants with BMI ≥ 30 kg/m^2), the results should be interpreted with caution.

Conclusions

AZD1222 administered in 2 IM injections was generally well-tolerated and had an acceptable safety profile in Japanese adult participants across all age groups (18 to 55 years, 56 to 69 years, and ≥ 70 years), and the number of SAEs reported between Day 58 and Day 365, in addition to the unsolicited AEs collected up to Day 57, was low.

In the AZD1222 group, antibody titers for the S and RBD antigens and for the nAb (pseudoneutralization) to SARS-CoV-2 increased substantially after the first dose of study intervention, increasing further after the second dose. Data show a slightly decreasing trend in titers with increasing age, although a large variability was observed in the individual titers, with overlap in confidence intervals between cohorts.

Mean antibody titers had dropped by Day 183, decreasing further by Day 365, due to the expected waning of humoral immunogenicity. By Day 365, mean titers of S- and RBD-binding antibodies remained above Baseline and Day 15 levels; however, a large proportion of participants had no measurable nAb (pseudoneutralization) at this time point.

Taking the above into account, these data suggest that AZD1222 elicits strong early immune responses against SARS-CoV-2 in the Japanese adult population across all the age groups; however, waning of immune responses, with neutralizing antibodies below the lower limit of quantification, was observed in a large proportion of participants by Day 365.