Clinical Study Report Synopsis	
Drug Substance	AZD1222
Study Code	D8111C00010
Edition Number	1.0
Date	14 August 2023
NCT Number	NCT 05057897

A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multicenter Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19

Study dates:

First subject enrolled: 31 January 2022

Last subject last visit: 19 April 2023

Date of early study termination: 10 February 2023; since the study could not recruit the required number of participants, the European Medicines Agency removed the requirement for this study.

The analyses presented in this report are based on a clinical data lock date of 30 May 2023.

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator:
PPD
Mahidol University
PPD Bangkok Thailand, 10700

Sponsor's Responsible Medical Officer:
PPD
AstraZeneca
PPD Cambridge,
CB2 8DU, United Kingdom

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

Study D8111C00010 was initiated to fulfill a regulatory commitment to the European Medicines Agency. As a result of increased COVID-19 vaccination rates globally, and particularly in the immunocompromised population, the study could not recruit the required number of unvaccinated/naïve participants. Therefore, the European Medicines Agency removed the requirement for this study and the study was terminated early. As only 10% of the intended number of participants were enrolled in the study, study results are presented in a synoptic clinical study report.

Study centers

Participants were enrolled in 1 site in Ukraine and 3 sites in Thailand.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Planned objectives and endpoints are described in the table below. Estimands are described in the statistical analysis plan (SAP) v2.0 dated 26 May 2023.

As the study was terminated prematurely due to recruitment challenges, analyses were streamlined. Objectives and/or endpoints not assessed are highlighted in grey in the table below.

Table S1 Objectives and endpoints

Objectives	Endpoints [a]
Primary Immunogenicity Objective	
• To characterize the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years.	1) SARS-CoV-2 specific titers 2) Seroresponse of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
Secondary Safety Objective	
• To characterize the reactogenicity and safety of a 3-dose primary vaccination series with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.	• Reactogenicity: Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222 by e-Diary • Incidence of unsolicited AEs for 28 days post dose after each vaccination • Incidence of SAEs, MAAEs, and AESIs from Day 1 post treatment to the last study visit • Absolute and change from baseline [b] for safety laboratory measures

Table S1 Objectives and endpoints

Objectives	Endpoints [a]
Secondary Immunogenicity Objectives	
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ transplant compared to immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with hematopoietic stem cell transplant compared to immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ cancer patients receiving cytotoxic chemotherapy compared to immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with chronic inflammatory disorders compared to immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with primary immunodeficiency compared to immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with any immunocompromised condition compared to immunocompetent participants	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To characterize the immunogenicity after a third dose in a 3 dose primary vaccination series with AZD1222 in immunocompromised adults ≥ 18 years.	1) SARS-CoV-2 specific titers 2) Seroresponse of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
• To describe the immunogenicity after the third dose in a 3-dose primary vaccination series with AZD1222 in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised participants compared to immunocompetent participants after a 2-dose primary vaccination.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline b)

Table S1 Objectives and endpoints

Objectives	Endpoints [a]
• To describe the immunogenicity of the AZD1222 vaccination between 28 days post second dose compared to 28 days post third dose, in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised and immunocompetent participants.	1) Ratio of SARS-CoV-2 specific GMT titers 2) Difference in seroresponse rates of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from 28 days post Dose 2 to 28 days post Dose 3)
• To characterize the immunogenicity after a third dose booster vaccination of AZD1222, administered 6 months after Dose 1 of a 2-dose primary vaccination with AZD1222, in immunocompetent adults ≥ 18 years.	1) SARS-CoV-2 specific titers 2) Seroresponse of SARS-CoV-2 specific titers (≥ 4-fold rise in titers from baseline [b])
Exploratory Objectives	
• To monitor the occurrence of COVID-19 in immunocompromised adults ≥ 18 years that have received 2 doses of AZD1222. • To further describe humoral and cell-mediated responses to AZD1222 following administration of AZD1222 in immunocompromised adults ≥ 18 years of age. • To explore underlying mechanisms should any thromboembolic events occur. • To explore correlations between anti-S, pseudo-neutralization, and ChAdOx1 nAb antibody titers.	• Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 • Hospital/ICU admissions and deaths associated with COVID-19 • Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigen • Intracellular cytokine staining and flow cytometry for T.cell responses over time. • Breadth and depth of BCR and TCR repertoire through immunosequencing over time • Magnitude of ChAdOx1 nAbs over time (GMTs/GMFRs, Seroresponse rate) • Magnitude of SARS-CoV-2 specific binding (anti-RBD) responses (GMT/GMFR/Seroresponse) over time. • Other exploratory assays for humoral and cellular immune responses based upon emerging safety, efficacy, and immunogenicity data • In the case of thrombosis in combination with thrombocytopenia, a series of additional in-depth investigations could be performed (refer to CSP Appendix D) • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 nAb antibody titers, 28 days after Dose 1 and 28 days after Dose 2

[a] Immunogenicity endpoints were analyzed for both binding (anti-S) and pseudo-neutralization titers.

[b] Baseline was defined as the last collection prior to the first dose.

AE = adverse event; AESI = adverse event of special interest; BCR = B-cell receptor; COVID-19 = coronavirus disease 2019; CSP = clinical study protocol; GMFR = geometric mean fold rise; GMT = geometric mean titer; ICU = intensive care unit; MAAE = medically attended adverse event; nAb = neutralizing antibody; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndromecoronavirus-2; TCR = T-cell receptor

Study design

This study was a Phase IV, open-label, non-randomized, multi-cohort, multicenter study of the immunogenicity and safety of AZD1222 for the prevention of coronavirus disease-19 (COVID-19) in previously unvaccinated immunocompromised adults aged ≥ 18 years.

The study was planned to involve a total of 6 cohorts, 5 immunocompromised cohorts and 1 immunocompetent cohort, all including adults ≥ 18 years. The immunocompromised cohorts were to include participants with immunocompromising conditions or on stable doses of immunocompromising therapeutics:

1 Solid organ transplant
2 Hematopoietic stem cell transplant
3 Solid organ cancer patients receiving cytotoxic chemotherapy
4 Chronic inflammatory disorders
5 Primary immunodeficiency

The study comprised of:

- A Screening period, which started up to 7 days prior to Day 1,
- A Vaccination/Follow-up period that lasted up to 364 days after Day 1, with:
  - Intramuscular (IM) administration of AZD1222 on:
    - Visit 1 (Day 1) for both immunocompromised and immunocompetent cohorts,
    - Visit 5 (Visit 1 + 28 days) for both immunocompromised and immunocompetent cohorts,
    - Visit 8 (Visit 5 + 28 days) for immunocompromised cohorts only,
    - Visit 9 (Visit 1 + 182 days) for the immunocompetent cohort only.
  - Follow-up visits performed as per Schedule of Activities. For additional details see clinical study protocol (CSP v4.0) Section 1.3.

Target subject population and sample size

A total of approximately 360 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike and nucleocapsid seronegative participants aged ≥ 18 years old at the time of signing the informed consent were planned to be enrolled (ie, approximately 60 participants per cohort).

The sample size was determined mainly for feasibility purposes, with consideration for acceptable precision around the geometric mean titer (GMT) and seroresponse rates for a single cohort. For additional details on acceptable precision to support the chosen sample size, refer to the CSP v4.0, Section 9.2.

Due to recruitment challenges from increasing COVID-19 vaccination rates globally, particularly in the immunocompromised population, the study could not recruit the required 360 unvaccinated/naïve participants. The European Medicines Agency removed the requirement for this study, which was terminated after 34 participants were enrolled.

Investigational product: dosage, mode of administration and batch numbers

The investigational product was AZD1222, also named ChAdOx1 nCoV-19 (used in previous clinical documentation) or Vaxzevria® (current trade name).

AZD1222 was administered as a 0.5 mL IM injection into the deltoid of the nondominant arm (5 × 1010 viral particles). Other injection sites could be used if necessary.

Batch numbers were: 21569, PJ0146, NP0145, and NP0150.

Duration of treatment

All participants were planned to receive 2 IM doses of AZD1222, separated by 4 weeks, on Day 1 and Day 29. Immunocompromised participants received a third dose (primary vaccination series) 4 weeks or more after Dose 2 with AZD1222. Immunocompetent participants were eligible to receive a third dose booster 6 months after Dose 1. The approved dose and regimen of AZD1222 were used in this trial.

Statistical methods

Analyses were conducted using SAS version 9.4 or higher according to SAP.

There was no formal statistical hypothesis testing planned for this study. Descriptive analyses supported evaluation of safety and immunogenicity, and qualitative comparison between cohorts. For continuous data, n (number of participants with available data), mean or geometric mean, standard deviation (SD) or geometric SD, median, minimum, and maximum values have been presented. For categorical data, the number and percentages of participants in each category have been presented. Summaries of immunogenicity data also included 95% confidence intervals around GMT and seroresponse rates.

Unless otherwise indicated, all immunogenicity summaries were planned to be presented by cohort (including the pooled immunocompromised cohort) based on the immunogenicity analysis set (IAS). For all immunogenicity endpoints, participants were censored at the date of first positive polymerase chain reaction test for SARS-CoV-2 infection/non-study COVID-19 vaccine administration/exclusionary restricted medication/missed study dose, whichever occurred first. All safety summaries were to be presented by cohort based on the safety analysis set (SAF), except laboratory listings that were to be presented on the full analysis set (FAS).

Study population

A total of 37 participants were screened and included in the All Participants Analysis Set, and 34 participants were included in each the FAS and the SAF (for definitions of the populations, refer to the SAP). Participants were mainly enrolled in Thailand: 21 participants in the immunocompetent cohort and 9 participants in the immunocompromised cohort. Two participants in each cohort were enrolled in Ukraine. Five participants discontinued the study early, 1 participant died, and 4 participants discontinued due to the PPD . Finally, 28 of the participants included in the SAF had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response and had at least one baseline and post-baseline record in immunogenicity data. Those participants were included in the IAS.

Among the 34 participants enrolled, 23 were immunocompetent and 11 were immunocompromised: 2 were in the "hematopoietic stem cell transplant" cohort, 4 each were in the "solid organ cancer patients receiving cytotoxic chemotherapy" and "chronic inflammatory disorders" cohorts, and 1 was in the "primary immunodeficiency" cohort. The proportion of participants who completed treatment was balanced between the pooled immunocompromised cohort (later referred to as the immunocompromised cohort) and the immunocompetent cohort with 6 participants (54.5%) in the immunocompromised cohort and 13 participants (56.5%) in the immunocompetent cohort. A total of 29 participants (85.3%) completed the study: 8 (72.7%) in the immunocompromised cohort and 21 (91.3%) in the immunocompetent cohort.

The two cohorts were not balanced in terms of age and gender. Participants in the immunocompromised cohort were older compared to those in the immunocompetent cohort (mean age of 57.1 years versus 38.6 years, respectively). There were more males (52.2%) in the immunocompetent cohort while there were more females (63.6%) in the immunocompromised cohort. However, the two cohorts were balanced in terms of body mass index (BMI) with a mean BMI of 23.36 kg/m² in the immunocompromised cohort and 23.50 kg/m² in the immunocompetent cohort. Differences in demographic characteristics can only be considered as descriptive and should be interpreted with caution due to the small sample size in each cohort.

Summary of immunogenicity results

As the study was terminated prematurely due to recruitment challenges, analyses were streamlined, and no summaries were produced by individual immunocompromised cohort. Hence, because of the small sample size in each cohort, no comparison was done between the different immunocompromised cohorts and the immunocompetent cohort, as well as between 28 days post Dose 2 compared to 28 days post Dose 3 in the immunocompetent cohort. The exploratory objective aiming to explore correlations between anti-S, pseudo-neutralization, and ChAdOx1 nAb antibody titers was also not assessed. Finally, intracellular cytokine

staining and flow cytometry for T-cell responses over time, breadth and depth of B-cell receptor and T-cell receptor repertoire through immunosequencing over time, and other exploratory assays for humoral and cellular immune responses based upon emerging safety, efficacy, and immunogenicity data were also not assessed.

Generally, caution should be taken with interpretation of results assessing the immunogenicity after Dose 3 due to the limited data available, in particular in the immunocompromised cohort (n=2).

In both cohorts, neutralizing antibody (nAb) titers were below the lower limit of quantitation at baseline in all study participants. The geometric mean titer (GMT) of nAbs (geometric standard deviation [GSD]) reached 47.7 (4.54) in the immunocompromised cohort compared to 67.9 (4.69) in the immunocompetent cohort after Dose 1; 122.0 (5.14) compared to 166.5 (2.58), respectively, after Dose 2; and 224.5 (1.37) compared to 710.3 (3.11), respectively, after Dose 3. The percentage of participants who reached seroresponse increased in both cohorts from post Dose 1 to post Dose 2 (22.2% to 62.5% in the immunocompromised cohort and 44.4% to 92.9% in the immunocompetent cohort) and from post Dose 2 to post Dose 3 (62.5% to 100% in the immunocompromised cohort and 92.9% to 100% in the immunocompetent cohort).

Anti-spike binding GMTs (GSDs) were 93.7 AU/mL (3.22) in the immunocompromised cohort and 45.7 AU/mL (4.43) in the immunocompetent cohort at baseline. The GMT (GSD) of anti-spike binding responses reached 3997.2 AU/mL (4.37) in the immunocompromised cohort compared to 19134.7 AU/mL (3.14) in the immunocompetent cohort after Dose 1; 13262.8 AU/mL (12.39) compared to 28320.9 AU/mL (1.71), respectively, after Dose 2; and 48303.4 AU/mL (1.32) compared 86462.9 AU/mL (2.56), respectively, after Dose 3. In the immunocompromised cohort, the percentage of participants who reached seroresponse was 88.9% after Dose 1, 75.0% after Dose 2, and 100% after Dose 3. In the immunocompetent cohort, the percentage of participants who reached seroresponse was 100% after Dose 1 and remained stable after Dose 2 and Dose 3.

Data on magnitude of ChAdOx1 nAbs and SARS-CoV-2 specific binding (anti-receptor binding domain) responses over time are available in appendices.

Summary of safety results

Unsolicited adverse events (AEs) were collected up to 28 days after each vaccination. Serious AEs (SAEs) were collected from date of informed consent through to the end of study, and medically attended AEs (MAAEs), AEs of special interest (AESIs), and COVID-19 related AEs were collected from date of first dose through to the end of study. Of note, the summary of unsolicited AEs should be interpreted with caution due to the low sample size.

Adverse events were more frequently reported in the immunocompromised cohort than in the immunocompetent cohort with 12 AEs reported in 8 participants (72.7%) and 21 AEs reported in 13 participants (56.5%), respectively.

Serious AEs - In the immunocompromised cohort, 1 participant (9.1%) had an SAE with an outcome of death. In the immunocompetent cohort, 4 SAEs were reported in 4 participants (17.4%). All 4 SAEs were COVID-19 related, 1 mild and 3 moderate in intensity, and resulted in AZD1222 discontinuation (these subjects did not receive Dose 3) but none resulted in study discontinuation, and all participants had recovered at the time of this report. All 5 SAEs were considered not related to AZD1222 by the Investigator.

Medically attended AEs – MAAEs occurred in 1 participant (9.1%, 1 event) in the immunocompromised cohort and 4 participants (17.4%, 4 events) in the immunocompetent cohort. Of the 5 MAAEs, 4 were SAEs due to COVID-19 (as described above) and 1 was due to a left ankle sprain. All were considered not related to AZD1222 by the Investigator, and none caused study discontinuation.

Adverse events of special interest – AESIs occurred in 5 participants (45.5%, 5 events) in the immunocompromised cohort and 9 participants (39.1%, 10 events) in the immunocompromised cohort. All AESIs were COVID-19 infections, mild to moderate (none were severe).

Adverse events leading to discontinuation of AZD1222 – 1 participant (9.1%) in the immunocompromised cohort and 8 participants (34.8%) in the immunocompetent cohort had an AE leading to discontinuation of AZD1222. None of these events were considered related to AZD1222 by the Investigator.

COVID-19 related AEs – COVID-19 related AEs were reported in 5 participants (45.5%, 5 events) in the immunocompromised cohort and in 9 participants (39.1%, 10 events) in the immunocompetent cohort. All 5 participants in the immunocompromised cohort who had COVID-19 had received 2 doses of vaccine. No events were associated with hospital or intensive care unit admission, nor resulted in participant’s death.

AEs other than COVID-19 related – When considered by preferred term, only COVID-19 related AEs were reported in more than 1 participant in each cohort. AEs other than COVID-19 related were reported in 1 participant each.

Distribution of solicited AEs was as expected. Solicited local and systemic AEs collected within 7 days of any vaccination were slightly more frequent in the immunocompetent cohort compared to the immunocompromised cohort. The difference arose from local AEs (63.6% versus 87.0%), while systemic AEs were balanced between the two cohorts (72.7% versus 69.6%). Pain and tenderness were the most frequently reported solicited local AEs in both

cohorts: 45.5% and 54.5%, respectively, in the immunocompromised cohort, and 87.0% and 78.3%, respectively, in the immunocompetent cohort. In the immunocompromised cohort, 1 participant reported erythema and 1 reported induration/swelling versus none in the immunocompetent cohort. In both cohorts, the most frequently reported solicited systemic AEs were muscle pain, headache, and malaise ranging from 45.5% to 54.5% in the immunocompromised cohort and from 47.8% to 60.9% in the immunocompetent cohort. Fatigue was reported less frequently in the immunocompromised cohort compared to the immunocompetent cohort (27.3% versus 52.2%).

The frequency of local and systemic AEs was higher after Dose 1 compared to after Dose 2 in both cohorts, even though the decrease was more pronounced in the immunocompetent cohort than in the immunocompromised cohort (from 54.5% to 45.5% in the immunocompromised cohort and from 91.3% to 52.2% in the immunocompetent cohort).

No summary tables were developed to describe absolute change from baseline for safety laboratory measures. Data available in a listing did not show any trend of clinically significant abnormality. Most of the abnormalities were present at time of screening and were expected for immunocompromised patients. No Hy's law cases were reported.

As no thromboembolic events occurred, underlying mechanisms were not explored.

Conclusions

This study was terminated owing to recruitment challenges. Therefore, the required number of participants could not be reached for sufficient statistical power.

The results showed that immunological responses to vaccination were lower in the immunocompromised cohort than in the immunocompetent cohort after each vaccination dose. However, in both cohorts, dose titers were increased after each vaccination compared to the previously measured titers showing the intended effect of the vaccination.

The safety profile was acceptable in both cohorts, with no SAEs or AEs leading to discontinuation of vaccination considered related to AZD1222 by the Investigator and the profile of solicited AEs was similar to what was previously reported.