Final Clinical Study Report Synopsis	
Drug Substance	AZD7442
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A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19

Final Report

Study dates: First participant enrolled: 21 November 2020
Last participant last visit: 16 August 2022
There were 5 data cut-offs (database locks) in the study: 05 May 2021 (13 August 2021), 29 June 2021 (05 October 2021), 29 August 2021 (25 October 2021), 13 April 2022 (10 May 2022), Final Analysis (22 February 2023)

Phase of development: Therapeutic confirmatory (III)

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

Study centres

This study was conducted in 87 study centers across the United States (US), United Kingdom (UK), Belgium, France, and Spain.

Publications

Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, et al; PROVENT Study Group. Intramuscular AZD7442 (tixagevimab-cilgavimab) for prevention of Covid-19. N Engl J Med. 2022;386(23):2188-2200.

Objectives and criteria for evaluation

Table S1 Objectives and Outcome Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183
Primary	Safety	To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo	AEs, SAEs, MAAEs, and AESIs post dose of IMP
Key Secondary	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	The incidence of participants who have a post-treatment response (negative at baseline to positive at a time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
Secondary	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP
Secondary	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP
Secondary	PK	To assess the PK of AZD7442 administered as a single dose of 300 mg IM	Serum AZD7442 concentrations. PK parameters if data permit.
Secondary	Immunogenicity	To evaluate ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum

Table S1 Objectives and Outcome Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366
Exploratory	PK	To evaluate the single dose PK concentrations of AZD7442 in nasal fluid	AZD7442 nasal concentrations Not reported in this CSR.
Exploratory	PD	To determine anti-SARS-CoV-2 nAb levels in serum following a single IM dose of AZD7442 or placebo	Post-treatment GMT and GMFR from baseline value through Day 457 after single IM dose in SARS-CoV-2 nAbs (wild-type assay or pseudo neutralization assay)
Exploratory	Efficacy	To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Viral genome copies in NP swabs at Illness Visits as determined by qRT-PCR
Exploratory	Efficacy	To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Duration of SARS-CoV-2 shedding in saliva over time
Exploratory	Efficacy	To characterize resistance to AZD7442 (Illness Visits)	Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442
Exploratory	Efficacy	To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Biophysical parameters, including, but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28
Exploratory	Efficacy	To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)	Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28

Table S1 Objectives and Outcome Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Immunogenicity	To assess additional immune responses following a single IM dose of AZD7442 or placebo	Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and PD data Not reported in this CSR.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CSR, clinical study report; GMT, geometric mean titers, GMFR, geometric mean fold rises; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically-attended adverse event; nAb, neutralizing antibody; NP, nasopharyngeal; qRT-PCR, quantitative real-time polymerase chain reaction; PD, pharmacodynamic; PK, pharmacokinetic(s); RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Study design

PROVENT was a Phase III, randomized, double-blind, placebo-controlled, multi-country, multicenter study assessing the safety and efficacy of a single 300 mg dose of AZD7442 (2 sequential intramuscular [IM] injections) compared to placebo for the prevention of coronavirus disease 2019 (COVID-19).

Participants at a subset of active PROVENT study sites in Belgium, UK, and the US were invited to enroll in a Phase III open-label substudy (D8850C002A01) to assess the safety, pharmacokinetics (PK), and immunogenicity of repeat doses of AZD7442. These participants completed the Day 366 visit and then left the main study to enroll into the substudy. The remaining participants in the PROVENT main study were to complete the study according to the study plan.

This report presents the results following a single dose of AZD7442 or placebo. The substudy is ongoing and the results from repeat dosing will be presented separately.

Target subject population and sample size

Participants were adults, ≥ 18 years of age, who were expected to benefit from receiving monoclonal antibodies (mAbs), defined as having an increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having an increased risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment.

Approximately 5150 participants were planned to be randomized in a 2:1 ratio to receive a single IM dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) or saline placebo in 2 sequential injections on Day 1 (approximately 3433 participants in the AZD7442 group and 1717 in the placebo group). Approximately 500 participants at a subset of active study sites in participating countries were invited to enroll in the substudy.

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

AZD7442 (cell pools material or clonal cell line material) was supplied as separate vials of AZD8895 and AZD1061 as 150 mg of each (300 mg total). The batch numbers were 008K20, 034K20, 041H20, and 042H20. Placebo was 0.9% (weight/volume) saline for injection. Investigational medicinal product (IMP) was administered as 2 consecutive IM injections, one in each gluteal region.

Duration of treatment

Single dose.

Statistical methods

The primary endpoint (variable) was a binary response, whereby a participant was defined as a COVID-19 case if their first case of SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)-positive symptomatic illness occurred post dose of IMP and prior to Day 183. If a participant's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred on or after Day 183, the participant did not meet the primary endpoint.

The primary analysis was planned after approximately 24 primary endpoint events had been confirmed across the active and control groups or 30% of study participants had become unblinded (at which point the ability to observe primary endpoint events was expected to have diminished), whichever occurred earlier. All primary endpoint events accrued up until the data cut-off were included in the primary analysis.

The primary efficacy was calculated as relative risk reduction (RRR), ie, 100% × (1-relative risk), which is the incidence of symptomatic infection in the AZD7442 group relative to the incidence of symptomatic infection in the control group, expressed as a percentage. Relative risk reduction was estimated from a Poisson regression model with robust variance. The model included arm and age at informed consent, with the log of the follow-up time as an offset. Efficacy summaries are presented with 2-sided 95% confidence intervals (CI). Statistical significance was achieved if the 2-sided p-value was < 0.05.

A hierarchical approach was used to control for multiplicity of the primary, key supportive, and key secondary analyses. The primary efficacy endpoint was assessed at the primary analysis, using the primary estimand. Nominal p-values are provided for the other secondary

and exploratory efficacy endpoints. No statistical testing was performed for the safety endpoints.

Data were produced at 5 different data cut-offs (DCOs) during the study. Data summarized are shown in Table S2.

Table S2 Data Cut-off Dates for the Analyses Contained in the Final CSR

DCO Date	Definition/data available in the CSR body	Short name
05 May 2021	Planned after approximately 24 primary endpoint events had been confirmed across the active and control groups or 30% of study participants had become unblinded. Efficacy (primary analysis)	Primary Analysis DCO
29 June 2021	Not presented in the CSR body	Not applicable
29 August 2021	Key efficacy tables [a] (median 6 months analysis; minimum of 5 months' data on all ongoing participants)	August 2021 DCO
13 April 2022	Not presented in the CSR body	Not applicable
22 February 2023 (Final DBL)	Final efficacy, safety, ADA, PK, exploratory endpoints	Final Analysis

[a] Primary, key supportive, and key secondary efficacy analyses.

The primary and final analyses were pre-specified in the CSP. All other DCOs were added in response to health authority requests; the June 2021 DCO was decided before the analysis team was unblinded for the primary analysis and the August 2021 and April 2022 DCOs were decided after the analysis team was unblinded for the primary analysis.

ADA, antidrug antibodies; CSP, clinical study prototype; CSR, clinical study report; DBL, database lock; DCO, data cut-off; PK, pharmacokinetics.

Study population

In total, 5254 participants were randomized and 5197 received IMP (3460 in the AZD7442 group and 1737 in the placebo group). A total of 5197 participants were included in the Full Analysis Set and Safety Analysis Set and 5172 were included in the Full Pre-Exposure Analysis Set. At the Primary Analysis DCO, 5109 (97.2%) participants were ongoing in the study and 145 (2.8%) participants had discontinued from the study; no participants had discontinued due to an adverse event (AE). At the Final Analysis, 3669 (69.8%) participants had completed the study, 503 (9.6%) had left the main study to participate in the substudy, and 1082 (20.6%) participants had discontinued from the study. Two (0.3%) participants in the AZD7442 group and 1 (0.3%) participant in the placebo group discontinued the study due to an AE.

In general, the demographic and other baseline characteristics were well balanced between the AZD7442 and placebo groups. The mean age of participants was 53.5 years and 43.4% were ≥ 60 years of age. A slightly higher proportion of participants were male (53.9%) than female (46.1%). Most participants were White (73.0%). In addition, 17.3% were Black/African

American, 14.5% were Hispanic or Latino, and 79.7% were not Hispanic or Latino. Mean body mass index was 29.59 kg/m^2. These demographic characteristics were representative of the regions in which the study was conducted and there were no relevant imbalances between the AZD7442 and placebo groups.

Per the exclusion criteria, all participants were COVID-19 vaccine naïve at enrollment. At the Primary Analysis DCO, approximately 30% of participants in both the AZD7442 and placebo groups had elected to be unblinded to make an informed decision about receiving a COVID-19 vaccine. Consistent with the different advice offered to the AZD7442 participants and placebo participants, a greater proportion of placebo participants had received a COVID-19 vaccine at the Primary Analysis DCO (12.3% for AZD7442 and 31.0% for placebo). At the Final Analysis, the difference between the groups was smaller (53.8% for AZD7442 and 61.1% for placebo).

With regards to baseline COVID-19 characteristics (ie, the potential condition under investigation), the SARS-CoV-2 RT-PCR status was negative for 95.8% participants, positive for 0.5% of participants and missing for 3.7% of participants. Participants who had a positive SARS-CoV-2 PCR test at baseline were excluded from the efficacy analyses. In all, 68.3% of the population presented with one or more comorbidities at baseline and 77.7% were at high risk for severe COVID-19 at baseline. The most common risk factors for severe COVID-19 were previous history of obesity (42.4%), current obesity (41.7%), hypertension (36.4%), smoking (21.0%), diabetes (14.3%), asthma (11.3%), and cardiovascular (CV) disease (8.2%). There were no relevant imbalances between the AZD7442 and placebo groups for these COVID-19 high risk factors.

Important protocol deviations occurred in 28.4% of the study population at the primary analysis and 51.5% at the Final Analysis; they were balanced between the AZD7442 and placebo groups at both data cuts and are not expected to have affected the analyses. No participants were excluded from the Full Analysis Set or Full Pre-exposure Analysis Set due to a protocol deviation.

Summary of efficacy results

The primary objective was met. There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received AZD7442 compared to placebo at the Primary Analysis DCO: RRR 76.73 (95% CI: 46.05, 89.96); $p < 0.001$. The median (range) duration from dose of IMP to Primary Analysis DCO was 83.0 (3 to 166) days.

Additional pre-specified analyses were conducted to assess both the impact of unblinding and/or vaccination on the primary result as well as on all-cause mortality; both analyses were consistent in the RRR estimates with the primary result indicating that neither the high

unblinding and vaccination rates nor the non-COVID-19 related deaths affected the analysis of this endpoint. Consistency in the RRR estimates were also observed across all the pre-specified subgroups, including those potentially at risk of inadequate protection to vaccines and those at higher risk of severe disease. The time to event analysis of the primary endpoint was also consistent with the primary analysis. When the primary efficacy analysis was repeated at the Final Analysis (when all participants had completed the efficacy evaluation period Day 1 to Day 183), the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received AZD7442 compared to placebo was consistent with the primary analysis: RRR 83.04 (95% CI: 67.26, 91.21); nominal $p < 0.001$.

For the key secondary endpoint, the incidence of post-treatment infection (negative at baseline and positive for post-baseline nucleocapsid antibodies) at Day 183 was significantly lower in the AZD7442 group (0.7%) than the placebo group (1.3%) at the Primary Analysis DCO: RRR 51.07 (95% CI: 10.57, 73.23); $p = 0.020$. When repeated at the Final Analysis, the incidence was 1.3% of participants for AZD7442 and 3.2% for placebo at Day 183 (RRR 61.15 [95% CI 41.72, 74.11]; nominal $p < 0.001$) and 6.3% participants for AZD7442 and 8.9% for placebo at Day 366 (RRR 34.90 [21.44, 46.05]; nominal $p < 0.001$).

No participants had SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness up to Day 183 in the AZD7442 group compared with 1 (0.1%) participant in the placebo group at the Primary Analysis DCO (secondary endpoint). When repeated at the Final Analysis, the corresponding numbers were 0 and 6 (0.3%) participants for AZD7442 and placebo, respectively, up to Day 183, and 2 (0.1%) and 11 (0.6%) for AZD7442 and placebo up to Day 366.

At the Primary Analysis DCO, 6 (0.2%) participants in the AZD7442 group and no participants in the placebo group had COVID-19-related emergency department visits up to Day 183 (secondary endpoint). When repeated at the Final Analysis, the proportion of participants with COVID-19-related emergency department visits were comparable between the AZD7442 and placebo groups up to Day 183 (0.2%) in both groups) and numerically lower in the AZD7442 group (0.2%) compared with the placebo group (0.5%) up to Day 366.

Exploratory efficacy analyses showed the following:

- AZD7442 reduced the risk of developing symptomatic COVID-19 through Day 366 compared to placebo: RRR 46.27 (95% CI: 23.14, 62.44; nominal p-value < 0.001).
- The most commonly reported COVID-19 symptoms were cough, fatigue, and congestion.

Summary of pharmacokinetic results

The geometric mean serum concentrations of AZD8895 and AZD1061 through Day 457 were similar. The observed PK profiles were consistent with antibodies with long half-lives of approximately 90 days.

The 90% CI of geometric mean ratios of AZD7442 maximum serum concentration (Cmax) and area under the plasma concentration-time curve (AUC) between cell pools and clonal cell line materials over 0 to 3 months, 0 to 6 months, and 0 to 12 months met the bioequivalence criterion of 80% to 125%.

Summary of immunogenicity results

Antidrug antibody (ADA) prevalence (% ADA positive) and ADA incidence treatment emergent-ADA (% TE-ADA+) of AZD7442 in the AZD7442 group (participants randomized to receive AZD7442) were 32.1% and 13.1%, respectively. For both component mAbs (AZD8895 and/or AZD1061) and AZD7442 in the AZD7442 arm, the majority of ADA positive participants were not classified as TE-ADA positive.

The median AZD7442 ADA titer remained low and unchanged at 80.0 (relative to the limit of detection of 40) throughout Day 457, suggesting no maturation of ADA over time. Over the same period, the range of median ADA titer to AZD7442 in the placebo arm was similar, indicating that ADA titers that resulted from AZD7442 administration were no different than those which resulted from placebo administration. ADA had no apparent effect on the PK and safety of AZD7442.

Summary of pharmacodynamic results

This study included an exploratory pharmacodynamic endpoint to determine anti-SARS-CoV-2 neutralizing antibody (nAb) levels in serum following a single IM dose of AZD7442 or placebo. At all time points evaluated, the geometric mean titers in participants who received AZD7442 exhibited > 6-fold increases in titer compared to baseline starting at Day 8 (19-fold increase) out to Day 366 (6-fold increase). In addition, nAb titer values remained 3-fold higher than those measured in patients convalescing after natural infection with SARS-CoV-2 one year after receiving AZD7442.

Anti-viral resistance

In line with AstraZeneca's ongoing effort to monitor for SARS-CoV-2 spike variants containing potential AZD8895, AZD1061, and AZD7442 (AZD8895 and AZD1061) resistance-associated substitutions in all clinical studies, an exploratory endpoint to assess anti-viral resistance was conducted as part of the PROVENT study. AZD7442 retained neutralizing activity against all variants of concern identified in study participants (including Alpha, Delta, Epsilon, and Omicron BA.1 and BA.1.1).

Summary of safety results

In total, 5197 participants were dosed with IMP during the study (3461 with AZD7442 and 1736 with placebo). The median duration of follow-up was 456 days in the AZD7442 group and 455 days in the placebo group. Note that participants were randomized at a 2:1 ratio to AZD7442 or placebo, respectively.

Overall, the frequency of AEs during the study was similar in the AZD7442 group compared with the placebo group (58.2% versus 58.0%, respectively). The most frequent AEs were COVID-19, headache, fatigue, and cough. There were no clinically relevant trends in the AE preferred terms (PTs) between the AZD7442 and placebo groups. Most of the AEs were Grade 1 or Grade 2 in severity and the proportions were similar between the AZD7442 and placebo groups.

The incidence of serious adverse events (SAEs) was 6.2% of participants for AZD7442 versus 5.6% for placebo. There was a numerical imbalance in SAEs in the Cardiac disorders system organ class (SOC) between AZD7422 and placebo (1.2% versus 0.5%). SAEs with PTs under the Cardiac disorder SOC or the standardized MedDRA query 'embolic and thrombotic events' (cardiac and thromboembolic SAEs) were reported by 1.6% of participants in the AZD7442 group and 0.9% of participants in the placebo group. Based on medical history at baseline, all participants who experienced cardiac or thromboembolic SAEs had cardiac risk factors and/or a prior history of CV disease and there was no clear clinical or temporal pattern. There were no discernible patterns or imbalances in the reporting of SAEs with mostly single events being reported in either or both the AZD7442 and placebo groups. Two of the 215 reported SAEs in the AZD7442 group were considered possibly related to IMP by the Investigator (chronic myeloid leukemia, mesenteric artery thrombosis). No SAEs in the placebo group were considered possibly related to IMP.

The number of participants with AEs leading to death was 22 [0.6%] in the AZD7442 group and 10 [0.6%] in the placebo group). None of the deaths were considered potentially related to IMP by the Investigator. The independent Morbidity Adjudication Committee considered 4 (0.1%) of the deaths in the AZD7442 group and 4 (0.2%) in the placebo group to be due to COVID-19.

The proportion of participants with adverse events of special interest (AESIs) during the study was similar for the AZD7442 and placebo groups (3.0% and 2.5%, respectively), and most of the reported AESIs were injection site reactions. The frequency of injection site reactions was similar between the AZD7442 group and the placebo group (2.4% versus 2.1%, respectively) and none were reported as SAEs. One event of anaphylaxis was reported in the AZD7442 group, but it did not meet the definition of anaphylaxis.

The proportion of participants with at least one medically-attended AE was similar between the AZD7442 (28.6%) and placebo groups (25.3%). The type and frequency of individual medically-attended AEs were generally similar between the AZD7442 and placebo groups.

An independent, external, systematic, and unbiased assessment of blinded data were conducted to verify whether reported CV events met pre-specified criteria for a CV event and whether fatal AEs involved CV deaths. Of the CV events in the AZD7442 group that were referred to the independent CV Event Adjudication Committee, 1.2% of participants in the AZD7442 group had events that met the pre-defined adjudication criteria for a positive CV event; and 1.6% of participants had events that did not meet the criteria. In the placebo group, 0.7% met the criteria and 1.8% did not.

No differences in the safety profiles were noted for participants who received cell pools material versus clonal cell line material (although the proportion of participants who received clonal cell line material was relatively small [2.7%]).

The final analysis of safety data was consistent with the findings from the earlier DCOs.

Conclusion(s)

- AZD7442 administered in a prophylactic setting reduced the risk of developing symptomatic COVID-19 by 76.73% compared with placebo (RRR 76.73, 95% CI 46.05, 89.96, $p < 0.001$; primary analysis). The result was consistent across all pre-defined subgroups including those potentially at risk of inadequate protection to vaccines and those at higher risk of severe disease. Further analyses of efficacy with longer duration of follow-up at the Final Analysis (RRR 83.04, 95% CI: 67.26, 91.21; $p < 0.001$) confirmed the findings from the primary analyses.
- The PK results were as expected based on the Phase I Study D8850C00001. The 90% CI of geometric mean ratios of AZD7442 Cmax and AUC between cell pools and clonal cell line materials met the bioequivalence criterion of 80% to 125%.
- The majority of ADA positive participants in the AZD7442 group were not classified as TE-ADA positive. The presence of ADA had no apparent effect on the PK and safety of AZD7442.
- The nAb levels supported the expected pharmacodynamic activity of AZD7442 and exceeded those reported in the literature for patients recovering from a SARS-CoV-2 infection by at least 3-fold for 12 months.
- There was a numerical imbalance in SAEs in the Cardiac disorders SOC between the treatment groups (40 [1.2%] versus 8 [0.5%] participants for AZD7442 and placebo, respectively). All participants with Cardiac disorder SAEs during the study had cardiac risk factors and/or a prior history of CV disease at baseline, and there was no clear temporal or clinical pattern.
- The results demonstrated an acceptable safety and tolerability profile for AZD7442. There were no SAEs of anaphylaxis, hypersensitivity, or injection site reactions.