Clinical Study Report Synopsis	
Drug Product	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 Post-exposure Prophylaxis of COVID-19

Final Report

Study dates:
First participant enrolled: 02 December 2020
Last participant last visit: 25 July 2022
There were 5 data cut-offs (database locks) in the study:

- 07 April 2021 (20 May 2021)
- 19 June 2021 (27 August 2021)
- 19 August 2021 (13 October 2021)
- 04 April 2022 (17 May 2022)
- Final (21 October 2022)

Phase of development: Therapeutic confirmatory (III)

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PPD

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

Study center(s)

This study was conducted in 60 centers across the United States (US) and the United Kingdom (UK).

Publications

Levin MJ, Ustianowski A, Thomas S, Templeton A, Yuan Y, et al, on behalf of the STORM CHASER Study Group, AZD7442 (Tixagevimab/Cilgavimab) for Post-exposure Prophylaxis of Symptomatic COVID-19, Clinical Infectious Diseases, 2022; doi.org/10.1093/cid/ciac899.

Objectives and criteria for evaluation

The objectives and endpoints for the study are summarized in Table S1.

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.	A binary response, whereby a participant was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred post dose of IMP and 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 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 SARS-CoV-2 infection.	The incidence of participants who had a post-treatment response (negative at baseline to positive at any 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 COVID-19-related death.	The incidence of COVID-19-related death occurring after dosing with IMP.

Table S1 Objectives and Outcome Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of all-cause mortality.	The incidence of all-cause mortality occurring after dosing with IMP.
Secondary	PK	To assess the pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM.	Serum AZD7442 concentrations. PK parameters if data permit.
Secondary	Safety	To evaluate ADA responses to AZD7442 in serum.	Incidence of ADA to AZD7442 in serum.
Exploratory	PK	To evaluate the single dose pharmacokinetic 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 GMTs and GMFRs from baseline value through Day 457 after single IM dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo neutralization assay).
Exploratory	Biomarker	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 or blood collected at Illness Visits as determined by qRT-PCR.
Exploratory	Biomarker	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 anterior nasal swabs over time.
Exploratory	Efficacy	To characterize resistance to AZD7442 (Illness Visits).	Genotypic analysis and biochemical, or susceptibility analysis of SARS-CoV-2 variants to AZD7442.
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	Immuno-genicity	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 have been performed based upon emerging safety, efficacy, and pharmacodynamic data. Not reported in this CSR.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; CSR, clinical study report; COVID-19, coronavirus disease 2019; GMFR, geometric mean fold rises; GMT, geometric mean titers; IM, intramuscular; IMP, investigational medicinal product; nAb, neutralizing antibody; MAAE, medically attended adverse event; NP, nasopharyngeal; PD, pharmacodynamic; PK, pharmacokinetic; qRT-PCR, quantitative reverse-transcriptase polymerase chain reaction; 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 Phase III, randomized, double-blind, placebo-controlled, multi-center study assessing the safety and efficacy of a single dose of AZD7442 (× 2 intramuscular [IM] injections) compared to placebo for the prevention of coronavirus disease 2019 (COVID-19). In total, 60 sites in the US and UK participated in this study.

Target participant population and sample size

Participants were adults, ≥ 18 years of age with potential exposure, within 8 days, to an index case (defined in the protocol as a specific identified individual with laboratory-confirmed severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2] infection, symptomatic or asymptomatic), who were therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment.

Up to 1125 participants were planned to be randomized in a 2:1 ratio to receive a single dose (× 2 IM injections) of either 300 mg of AZD7442 (n = approximately 750) or saline placebo (n = approximately 375) on Day 1. Enrollment was to be stopped after the 25th primary endpoint event had been confirmed, or after 1125 participants had been randomized, whichever occurred first.

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

AZD7442 (cell pools material) was supplied as separate vials of AZD8895 and AZD1061 as 150 mg of each (300 mg total). Placebo was supplied as 0.9% (weight/volume) saline for injection. Investigational medicinal product (IMP) was administered as 2 IM injections, one in each gluteal region.

The batch numbers for AZD7442 used in this study were A03498 and A03689.

Placebo was not provided by the Sponsor.

Duration of treatment

Single dose.

Statistical methods

The primary endpoint was the first case of SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR)-positive symptomatic illness occurring post dose of IMP and prior to Day 183. 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 RT-PCR-positive symptomatic illness occurred post dose of IMP prior to Day 183.

The primary analysis was assessed 30 days after the 25th event had occurred with a Poisson regression model that included the planned treatment group and the log of follow-up time as an offset. All primary endpoint events accrued until the data cut-off (DCO) were included in the primary analysis. The planned DCO for this primary analysis occurred on 07 April 2021.

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 cut-offs used in this report

Data were produced at 5 different DCOs during the study. Data summarized are shown in Table S2.

Table S2 Summary of the Different Data Cut-offs Included in the Final CSR

DCO Date	Definition/Endpoints	Short Name
07 April 2021	Primary efficacy analysis, performed 30 days after the 25th event had occurred. Includes primary endpoint, secondary endpoint	Primary Analysis DCO
19 June 2021	Not presented in the CSR body	Not applicable
19 August 2021	Not presented in the CSR body	Not applicable
04 April 2022	Not presented in the CSR body	Not applicable
Not applicable	Final efficacy, safety, ADA, PK, exploratory endpoints	Final Analysis

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.

DCO, data cut-off; PK, pharmacokinetic.

Participant population

At the time of the primary efficacy analysis (April 2021 DCO), 1131 participants were randomized, 1121 had received IMP, and 1110 were ongoing or completed the study. Twenty-one participants had discontinued from the study; no participants discontinued due to an AE. A total of 1121 participants were included in the full analysis set (primary efficacy analysis) and the safety analysis set. At the final analysis, no participants were ongoing in the study, 928 (82.1%) completed the study, and 203 (17.9%) participants had discontinued from the study. No participants in either group discontinued the study due to an AE.

Although the study originally intended to recruit up to 80% of its population from long-term care facilities (LTCFs), the rapid roll out of effective vaccines meant that only 0.9% of study participants were residents in LTCF. The mean age was 46.4 years (standard deviation [SD] 15.89) and most participants (80.0%) were younger than 60 years of age. The population was reasonably balanced between the sexes. The majority were White (84.1%). Regarding ethnicity, 57.5% were Hispanic or Latino and 40.9% were not Hispanic or Latino. These and other demographic characteristics such as smoking status, body mass index data and Eastern Cooperative Oncology Group performance status were as expected in the general population, and there were no relevant imbalances between the randomized treatment groups.

With regards to baseline COVID-19 characteristics (ie, the potential condition under investigation), 4.3% of participants were SARS-CoV-2 RT-PCR-positive at baseline, and 87.2% were SARS-CoV-2 RT-PCR-negative at baseline. In all, 56.0% of the population presented with some COVID-19 comorbidities at baseline, the most common (> 10%) previous history of obesity (40.1%), previous history of high blood pressure (23.9%), and history of Type 2 diabetes (11.6%).

Important protocol deviations occurred in 10.3% of the study population at the primary analysis and 40.9% at the final analysis, the vast majority of which were related to missed visits or visits outside time windows. They were balanced between treatment groups at both data analyses and did not affect the analysis. No participants were excluded from the full analysis set due to a protocol deviation.

Summary of efficacy results

The primary objective was not met. At the primary analysis DCO, the relative risk reduction (RRR) in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness was 33.31 (95%

confidence interval [CI]: -25.92, 64.68) for AZD7442 compared with placebo, which was not statistically significant (p = 0.212). The median (min, max) duration from dose of IMP to primary analysis for AZD7442 group was 49.0 (5, 115) days and 48.0 (20, 113) days for the placebo group.

The results for a pre-specified subgroup analysis found a nominally significant RRR for the subgroup of SARS-CoV-2 RT-PCR status negative or missing at baseline. For this subgroup, RRR was 73.17 (95% CI: 27.10, 90.13); there were 6/715 (0.84%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the AZD7442 group compared to 11/358 (3.07%) participants in the placebo group. There was no significant difference for other subgroups including age, sex, race, ethnicity, COVID-19 comorbidities at baseline or risk of COVID-19 at baseline.

When the pre-specified subgroup analysis for SARS-CoV-2 RT-PCR status negative or missing at baseline participants was repeated at the Final Analysis, the RRR was 70.16 (95% CI: 36.63, 85.95); there were 11/715 (1.54%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the AZD7442 group compared to 18/358 (5.03%) participants in the placebo group. There was no difference for other subgroups including age, sex, race, ethnicity, COVID-19 comorbidities at baseline or risk of COVID-19 at baseline.

For the key secondary endpoint from the primary analysis, only one event of SARS-CoV-2 RT-PCR-positive severe or critical illness occurred (in the placebo group) therefore no meaningful analysis or conclusion could be drawn on the effect of AZD7442 on severe or critical symptomatic illness in this setting.

For the key secondary endpoint from the final analysis, 2 events of SARS-CoV-2 RT-PCR-positive severe or critical illness occurred (in the placebo group) therefore no meaningful analysis or conclusion could be drawn on the effect of AZD7442 on severe or critical symptomatic illness in this setting

Exploratory analyses showed the following:

- Geometric mean titers of neutralizing antibody (nAb) were higher through at least Day (D)183 in AZD7442 study participants as compared to peak nAb responses observed during COVID-19 illness in placebo study participants.
- The most commonly reported COVID-19 symptoms were cough, fatigue, and headache.

Summary of pharmacokinetic results

The geometric mean serum concentrations of AZD8895 and AZD1061 through D457 were similar. The observed PK profiles confirm the long half-lives of the 2 antibodies.

Summary of immunogenicity results

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 of maximum ADA titers to AZD8895 and AZD1061 in TE-ADA+ participants in the AZD7442 arm were both 160, relative to the limit of detection of 80 and 40, respectively. The corresponding titers in TE-ADA+ participants in the placebo arm were numerically similar at 160 and 240, respectively, indicating that ADA titers resulting from AZD7442 administration were no different than those resulting from placebo administration. ADA had clear clinically relevant effect on AZD7442 PK. None of the AZD7442 TE-ADA+ participants who had at least one ADA titer to AZD8895 and/or AZD1061 ≥ 1280 had reported AEs of hypersensitivity or anaphylaxis, or injection site reactions.

Summary of pharmacodynamic results

This study included an exploratory pharmacodynamic endpoint to determine anti-SARS-CoV2 nAb levels in serum following a single IM dose of AZD7442 or placebo. Baseline nAb responses were low in all participants and, at all-time points evaluated, the GMFR in participants who received AZD7442 was increased in titer compared to baseline, peaking 28 days post administration (Geometric Mean Fold Rise (GMFR)=64.1 at D29). In addition, nAb responses were observed in participants with symptomatic illness in both the AZD7442 and placebo groups, with responses peaking at IL-D28 in both study arms (Geometric Mean Titer (GMT)=640.0 and 146.4 respectively). This indicates that the levels of nAb following AZD7442 administration were higher through at least 6 months post dosing than published levels seen in patients convalescing after natural infection with SARS-CoV-2. Moreover, AZD7442 did not prevent the formation of a humoral response to SARS-CoV-2 upon breakthrough infection.

Anti-viral resistance

The emergence of viral variants was analyzed as an exploratory endpoint in this study. At the 6-month follow-up, the most common variants observed were Alpha and Delta, with ancestral strain sequences also being observed. Relative response rates were similar between cases which had evaluable sequencing data and those that did not have evaluable sequencing data, however caution is warranted in the interpretation of case incidence for each individual lineage given the small sample size and the lack of sequencing data for all participants with SARS-CoV-2 infections. At the 12-month follow-up, 18 events of the Omicron variant were observed as well as additional cases of Delta. AZD7442 has previously been shown to have neutralization activity against all variants of concern at the time of the final analysis, including Alpha, Delta, and Omicron BA.1 and BA.1.1.

Summary of safety results

Overall, at the final analysis, the frequency of AEs during the study was lower in the AZD7442 group compared with the placebo group (46.5% versus 51.9%, respectively). The most frequent AEs were COVID-19, headache, fatigue, and cough. There were no clinically relevant trends in the AE preferred terms between treatment arms. The majority of the AEs had a maximum intensity of mild or moderate.

The proportion of participants who reported severe or life-threatening AEs was lower in the AZD7442 group compared with the placebo group (severe AEs: AZD7442 3.5%, placebo 5.6%, life-threatening AEs: AZD7442 0.1%, placebo 0.8%). The incidence of AEs leading to death was 0.4% versus 0.5%, respectively, with no imbalance between treatment arms. None of the AEs leading to death were assessed as related to IMP by the Investigator. There was no pattern or emerging trend in the reporting of severe or life-threatening AEs, with the majority of the AE PTs reported by only one participant per group.

The incidence of SAEs was 2.7% for AZD7442 versus 4.3% for placebo. There was no discernible pattern or emerging trend in the reporting of SAEs with mostly single events being reported in either or both treatment groups. None of the SAEs were considered possibly related to the IMP by the Investigator. There were 2 (0.3%) and 2 (0.5%) SAEs of Cardiac disorders for the AZD7442 group and the placebo group respectively.

For adverse events of special interest, there were no reports of hypersensitivity. Injection site reactions were reported by 0.5% and 1.1% of participants in the AZD7442 and placebo groups, respectively. The proportion of participants with at least one medically attended adverse event was similar between the AZD7442 (12.7%) and placebo groups (14.0%). The type and frequency of individual medically attended adverse events were generally similar between the AZD7442 and placebo groups.

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

Conclusions

- The primary endpoint of this study, which included all participants irrespective of SARS-CoV-2 RT-PCR status at baseline, did not show a statistically significant reduced risk of developing symptomatic COVID-19 for AZD7442 compared with placebo. However, AZD7442 did reduce the risk of developing symptomatic COVID-19 by 73.17% for the predefined analysis of a subgroup of participants with a negative or missing SARS-CoV-2 RT-PCR at baseline.
- The PK results were as expected based on a previous Phase I and PROVENT clinical studies.
- The majority of ADA positive participants in the AZD7442 arm were not classified as TE-ADA positive. ADA had no clear clinically relevant effect on AZD7442 PK. There is no apparent effect of ADA on the safety of AZD7442.

- The nAb levels supported the expected PD activity of AZD7442 and exceeded those reported in the literature for patients recovering from a SARS-CoV-2 infection and were above the IL-D28 titers through at least 6 months (D183).
- No safety signals or concerns were observed during the study. The results demonstrated an acceptable safety and tolerability profile for AZD7442, including a few observed injection site reactions, and no hypersensitivity reactions.