Final Clinical Study Report	
Drug Substance	AZD7442
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A Phase I Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AZD7442 in Healthy Chinese Adults

Final Report

Study Dates: First subject enrolled: 09 October 2021
Last subject last visit: 16 January 2023
The Primary Analysis data cut-off was 27 November 2021
The Interim Analysis data cut-off was 10 June 2022
The analyses presented in this report are based on a final clinical data lock date of 09 March 2023

Phase of Development: Clinical pharmacology (I)

Principle Investigator: PPD PPD

Co-ordinating Investigator: PPD PPD

Sponsor's Responsible Medical Officer: PPD PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study Centers

In total, 256 healthy participants were enrolled, 61 participants were randomized to a treatment group, and 60 participants were administered investigational product at 2 study centers in China.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

The primary and secondary objectives and endpoints are summarized in Table 1.

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of AZD7442 administered IM or IV to healthy Chinese participants 18 to 55 years of age	AEs, SAEs, AESIs, safety laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
Secondary	
To evaluate the serum PK of AZD8895 and AZD1061 after a single dose of AZD7442 administered IM or IV	Where possible, PK parameters were to be assessed for individual mAbs (AZD8895 and AZD1061): • After IM injection: Cmax, tmax, AUC(0-30days) • After IV infusion: Cmax, AUC(0-30days) • Additional PK parameters to be determined when appropriate include: AUClast, AUCinf, t½λz, tlast, CL, CL/F, Vz, Vz/F, Vss, and F
To evaluate the ADA responses to AZD7442 in serum	Presence of ADA to AZD8895 and AZD1061 in serum

Exploratory objectives and endpoints are not included in this Synopsis but are described in the clinical study report.

ADA, antidrug antibodies; AE, adverse event; AESI, adverse event of special interest; AUC(0-30days), area under the concentration-time curve from time zero to 30 days post-dose; AUCinf, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from time zero to time of last measurable concentration; CL, clearance; CL/F, apparent clearance after extravascular administration; Cmax, maximum concentration; ECG, electrocardiogram; F, bioavailability; IM, intramuscular; IV, intravenous; PK, pharmacokinetics; SAE, serious adverse event; t½λz, terminal elimination half-life, estimated as (ln2)/λz; tlast, time of last quantifiable concentration; tmax, time to maximum concentration; Vss, volume of distribution at steady state; Vz, volume of distribution based on terminal phase; Vz/F, volume of distribution based on terminal phase after extravascular administration.

Study Design

Study D8850C00007 was a Phase I, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD7442 in healthy Chinese volunteers aged 18 to 55 years.

Eligible participants were randomly assigned (ratio 4:1) to receive a single dose of either AZD7442 or placebo, administered intramuscularly (IM) or intravenously (IV), across 4 fixed-dose cohorts (15 participants per cohort):

- Cohort 1: 300 mg IM AZD7442 or placebo
- Cohort 2: 600 mg IM AZD7442 or placebo
- Cohort 3: 300 mg IV AZD7442 or placebo
- Cohort 4: 600 mg IV AZD7442 or placebo

Within each dose level, administration of AZD7442 and placebo was double-blinded. However, due to the difference in dose volumes and administration routes, dose levels were not blinded.

Participants were randomized and dosed on Day 1, then discharged on Day 2 (following completion of the 24-hour procedures). Participants were followed for approximately 15 months after dosing (through Day 451). Procedures at follow-up study visits included safety monitoring and collection of blood samples for PK and antidrug antibody (ADA) analyses.

This study had 3 planned analysis points:

- Primary Analysis: After all participants completed follow-up through Day 31.
- Interim Analysis: After all participants completed follow-up through Day 181.
- The final analysis: After all participants completed the study; follow-up through Day 451.

Investigators and participants remained blinded to the assigned IP until the end of the study. The Sponsor was unblinded after the primary database lock to perform the analysis for the report of the Primary Analysis and the Interim Analysis results (reported in the interim clinical study report, dated 29 August 2022).

Target Population and Sample Size

The target population was healthy Chinese volunteers 18 to 55 years of age. Participants needed negative results of both quantitative reverse transcription polymerase chain reaction (qRT-PCR) and serology tests for SARS-CoV-2 within 14 days before randomization.

The planned sample size was approximately 60 participants. No sample size calculation was performed based on hypothesis testing because descriptive statistics were used for the key endpoint assessments. The sample size was based on regulatory requirements and practical considerations that 8 to 12 participants needed to complete each active treatment for the key assessments.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

AZD7442 is a combination product of 2 monoclonal antibodies (mAbs), AZD8895 (tixagevimab) and AZD1061 (cilgavimab). A single dose comprises both mAb components administered in a fixed 1:1 ratio. Doses of AZD7442 are defined as the total mAb dose administered, eg, AZD7442 600 mg = AZD8895 300 mg + AZD1061 300 mg. AZD7442 doses were administered:

- Cohort 1: 300 mg IM sequential direct gluteal injections AZD7442 (150 mg AZD8895 and 150 mg AZD1061)
- Cohort 2: 600 mg IM sequential direct gluteal injections AZD7442 (300 mg AZD8895 and 300 mg AZD1061)
- Cohort 3: 300 mg IV co-administration (150 mg AZD8895 and 150 mg AZD1061)
- Cohort 4: 600 mg IV co-administration (300 mg AZD8895 and 300 mg AZD1061)

The batch numbers for AZD7442 used in this study were CCI [redacted].

Placebo was supplied as 0.9% (weight/volume) saline for matched injection or infusion.

Duration of Treatment

Single dose.

Statistical Methods

No statistical hypotheses were evaluated based on formal statistical tests. Descriptive statistics were presented for relevant data and parameters. Categorical variables were summarized using frequency and percentages. Continuous variables were summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles as appropriate.

Primary Endpoint: Safety and Tolerability. The primary endpoint analysis evaluated the safety and tolerability of AZD7442 based on summaries of adverse events (AEs), safety laboratory parameters, vital signs, and electrocardiogram (ECG) results. For the primary endpoint analyses, the data were presented by AZD7442 treatment groups (300 mg IM, 600 mg IM, 300 mg IV, 600 mg IV) along with a pooled AZD7442 group ("AZD7442 total

group") and a pooled placebo group ("pooled placebo group"). Certain AE analyses were additionally presented by route of administration (AZD7442 IM, AZD7442 IV, Placebo IM, Placebo IV).

Secondary Endpoint: Serum PK. Serum concentrations of the mAbs comprising AZD7442 (AZD1061 and AZD8895) were summarized by treatment group and time point using descriptive statistics. The actual dose of AZD7442 received was used for dose classification. PK data were tabulated for AZD7442 as well as the individual mAb components (AZD8895 and AZD1061).

Secondary Endpoint: ADA Responses. Results for antidrug antibodies (ADA) to AZD8895, AZD1061, and AZD7442 were reported individually. A participant was considered ADA-positive to AZD7442 if the participant had a positive ADA result to AZD8895 and/or AZD1061 at baseline or post-baseline. By-visit ADA titers were reported for participants with positive results and maximum titers observed were summarized. ADA results were also summarized by categories that considered whether positive results were treatment-emergent (TE) or persistent.

Study Population

There were 256 healthy participants who enrolled in the study, 61 participants were randomized, and 60 participants received the single dose of investigational product (IP; AZD7442 or placebo) on Day1. One participant randomized to a placebo group was withdrawn from the study due to an AE before receiving IP and is not included in the safety ADA, PK, PD and efficacy analysis sets.

The study participants were representative of the target population for this study: healthy volunteers in China, aged 18 to 55 years. In the Safety Analysis Set, the participants were Chinese adults, aged PPD to PPD years (mean PPD years), and 76.7% were men and 23.3% were women. Across the treatment groups, baseline characteristics were generally well-balanced.

As a result of regional lockdowns for COVID-19, some participants had disruptions to their visit schedules. Most disruptions were minor and not considered important protocol deviations. However, 3 participants in the IM cohorts missed a visit (Visit 11 [Day 181 ± 5] for 2 participants and Visit 12 [Day 271 ± 10] for one participant) because they were unable to return to study site before the protocol-specified visit window for the next. The missed visits were important protocol deviations but did not impact the overall study population profile or any conclusions for the final analysis.

Summary of Pharmacokinetic Results

Following IM administration; maximum serum concentrations for component mAbs (AZD8895 and AZD1061) were achieved at median tmax of approximately 6 to 14 days post-dose.

Cmax, AUClast, and AUCinf were similar for the 2 mAbs.

Geometric mean PK exposure (Cmax, AUC0-30, AUClast, and AUCinf) for AZD7442 increased in a nearly dose-proportional manner following IM administration of 300 mg and 600 mg AZD7442 (approximately 1.5- to 1.8-fold increases in geometric mean Cmax and AUCs) and in a dose-proportional manner following IV infusion of 300 mg and 600 mg AZD7442 (approximately 1.9- to 2.0-fold increases in geometric mean Cmax and AUCs).

The absolute bioavailability of AZD7442, calculated as the ratio of geometric mean AUC0-30, AUClast, and AUCinf, was approximately 68% to 75% for 300 mg IM and 55% to 71% for 600 mg IM.

Summary of ADA Results

The AZD7442 ADA incidence in the AZD7442 total group was 6.1% (3/49); all 3 participants were classified as TE and persistently ADA positive. ADA titers to AZD7442 in TE-ADA-positive participants were generally low, ranging from 80 to 640. There were no apparent impacts to PK or safety from the presence of ADAs.

The percentage of ADA positive participants in the pooled placebo group was 9.1% (1/11) for each component antibody. One participant was ADA positive at baseline (titer 80) and Day 15 (titer $\leq$ 80) for AZD8895 only, and one participant was ADA positive at all timepoints including baseline (titers of 40 or 80) for AZD1061 only. The ADA positive rate was numerically similar to that in the AZD7442 total group.

Summary of Safety Results

Across the AZD7442 groups, 45 (91.8%) participants had at least one AE; in the pooled placebo group 9 (81.8%) participants had at least one AE. Most AEs were mild in intensity.

In the AZD7442 total group, the most common AEs by PT were COVID-19 (24 [49.0%] participants), upper respiratory tract infection (12 [24.5%] participants), fatigue (7 [14.3%] participants), blood creatinine increased, cough, headache, lymphocyte percentage decreased, neutrophil count increased, rhinorrhea (4 [8.2%] participants each), alanine aminotransferase increased, diarrhea, neutrophil percentage increased, and white blood cells urine positive (3 [6.1%] participants each). In the placebo group 3 (27.3%) participants had AEs of COVID-19 and upper respiratory tract infection, and 2 (18.2%) participants had AEs of blood creatinine increased; all other PTs were experienced by one participant.

COVID-19 related AEs (including COVID-19, asymptomatic COVID-19, and suspected COVID-19) were reported in 27 (55.1%) participants who received AZD7442 and 3 (27.3%) participants who received placebo; however, the AZD7442 cases were spread across the individual AZD7442 groups (300 mg IM, 5 [41.7%]; 600 mg IM, 6 [50.0%]; 300 mg IV, 8 [66.7%], 600 mg IV, 8 [61.5%]). When comparing the individual AZD7442 groups with placebo, the difference between groups was less clear. The numbers of participants in each AZD7442 group were small, so no inference can be made when compared with the pooled placebo group. It is known that AZD7442 provides prophylaxis from symptomatic COVID-19 up to approximately Day 183 post-dose. For 29 of the 30 participants with COVID-19 related AEs in the study, the onset date of their first COVID-19 related AE was late in the study (with onset dates from Day 364 onwards), after the time that AZD7442 would be expected to prevent AEs associated with COVID-19 (ie, after Day 183). Among the 29 participants with COVID-19 starting after Day 183, 3 participants were in the pooled placebo group and 26 participants were in the AZD7442 total group. One participant (AZD7442 600 mg IM) had a COVID-19 related AE that started before Day 183.

There were no AEs leading to discontinuation/interruption of treatment or withdrawal from study, and no deaths. There were 2 non-IP related SAEs (a case of appendicitis and a case of inguinal hernia). One adverse event of special interest (injection site erythema) was reported in a participant in the AZD7442 600 mg IM group. The event was mild in intensity and resolved the same day without treatment.

No clinically meaningful trends in hematology, clinical chemistry, coagulation, urinalysis, vital signs, or ECGs were identified.

Conclusions

- Overall, a single dose of AZD7442 300 mg IM, 600 mg IM, 300 mg IV, or 600 mg IV was well tolerated in healthy Chinese participants over at least 442 days of follow-up (approximately 15 months).
- PK exposure increased nearly dose proportionally from 300 to 600 mg AZD7442 for IM administration, and dose proportionally for IV administration. The absolute bioavailability of AZD7442 was approximately 68% to 75% for 300 mg IM and 55% to 71% for 600 mg IM.
- Three participants who received AZD7442 were classified as TE and persistently ADA-positive. ADA titers to AZD7442 in TE-ADA-positive participants were generally low. The presence of ADAs did not appear to impact PK or safety outcomes for these participants.