Clinical Study Report Synopsis	
Drug Substance	AZD7442
Study Code	D8850C00008
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A Phase II Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults Primary Report

Study dates: First subject enrolled: 03 December 2021
Last subject enrolled: 24 January 2022
Last subject visit: Ongoing
The analyses presented in this report are based on:
Data cut-off date: 15 August 2022 (Primary Analysis)
Clinical data lock date: 17 October 2022

Phase of development: Therapeutic exploratory (II)

National Co-ordinating Investigator: PPD PPD

Coordinating Principal Investigator: PPD PPD

Sponsor's Responsible Medical Officer: PPD

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

Study center(s)

This is an ongoing study being conducted in 14 centers in mainland China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥ PPD of age at 6 months after administration	• 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 safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥ PPD of age at 15 months after administration [a]	• 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)
• To evaluate the serum PK of AZD8895 and AZD1061 after a single dose of 600 mg AZD7442 administered IV	Where possible, PK parameters will be assessed for individual mAbs (AZD8895 and AZD1061): • Cmax, AUC(0-180days) • Additional PK parameters that may be determined when appropriate include: ° AUClast, AUCinf, t½λz, tlast, Vss, Vz, and CL
• To evaluate the ADA responses to AZD7442 in serum	Presence of ADA to AZD8895 and AZD1061 in serum. • Blood samples will be collected and stored for analysis of ADAs. Unscheduled samples for ADA analysis may be collected in response to suspected immune-related AEs.

[a] Secondary objective of safety and tolerability at 15 months after administration will be assessed at the final DBL; these results are not included in this report.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; AUC(0-180days), area under the concentration-time curve from time zero to 180 days; 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; Cmax, maximum concentration; DBL, database lock; ECG, electrocardiogram; IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics; SAE, serious adverse event; t½λz, terminal elimination half-life, estimated as (ln2)/λz; tlast, time of last quantifiable concentration; Vss, volume of distribution at steady state; Vz, volume of distribution based on terminal phase.

Study design

This is a Phase II, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD7442 in Chinese adult participants ≥ PPD of age, including healthy participants as well as participants with stable medical conditions. Eligible participants were randomized (3:1 ratio) using Interactive Response Technology/Randomization and Trial Supply Management to receive a single dose of study intervention administered intravenously (IV), either 600 mg AZD7442 or placebo. Randomization was stratified by CCI [redacted].

This is an ongoing study. This CSR includes the Primary Analysis based on the data cut-off of 15 August 2022 and primary database lock (DBL) on 17 October 2022. The Primary Analysis was prespecified in the clinical study protocol to occur after all treated participants had completed follow-up through Day 181.

Target population and sample size

The target population was Chinese adults ≥ PPD of age, including healthy participants as well as participants with stable medical conditions.

The planned sample size for this study was 272 participants to be randomized 3:1 to the AZD7442 600 mg IV group (N = 204) or the placebo group (N = 68). If the true adverse event (AE) rate is 1% at the primary time point (ie, Month 6), 162 participants in the AZD7442 group would provide a probability of at least 80% to observe at least one AE case. A dropout rate of 20% was assumed. The 1% assumption was driven by the international convention where 1% is used as the lower limit of common AEs (between infrequent and frequent AEs).

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

AZD7442 was supplied as separate vials of AZD8895 and AZD1061 as sterile, clear to opalescent, colorless to yellow solutions. Placebo was supplied as sterile solution of 0.9% (w/v) sodium chloride for injection. Investigational medicinal product (IMP) was administered as a single IV infusion.

The batch numbers for AZD7442 used in this study were A03893 for AZD8895 and A03892 for AZD1061. Placebo was provided locally by the study site or by the sponsor.

Duration of treatment

Single dose.

Statistical methods

No statistical hypotheses were evaluated based on formal statistical tests. Descriptive statistics are presented for relevant data and parameters.

The primary analysis was to be conducted after all treated participants had completed follow-up through Day 181 or were withdrawn from the study. No early stopping decision was planned to be made for futility or superiority at the primary analysis. The final analysis will be conducted when all participants have completed the study (ie, completed follow-up through Day 451) or are withdrawn from the study.

Study population

In total, 272 participants were randomized 3:1 to AZD7442 (N = 202) and placebo (N = 70) from 14 centers in China; all 272 participants were included in the Safety, PK, and ADA analysis sets. At the time of the Primary Analysis data cut-off (DCO) (15 August 2022), all participants had completed the single administration of IMP and are being followed with ongoing visits, with the exception of 3 (1.1%) participants who withdrew early from the study. The mean age of participants was 34.2 years and were all Asian; 5.9% were over PPD of age and 69.1% were male. A total of 51.5% were COVID-19 vaccinated prior to study enrollment. In general, the demographic and baseline characteristics were well balanced between treatment groups and the study population was representative of the intended target population.

Summary of pharmacokinetic results

Following IV infusion of AZD7442 600 mg, the serum concentrations of AZD8895 and AZD1061 rapidly achieved the maximum values CCI and thereafter slowly declined. The geometric mean serum concentrations of the 2 component mAbs, AZD8895 and AZD1061, were similar over the sample collection period. The PK parameters (geometric mean [geometric coefficient of variation%]) of AZD8895 and AZD1061 were also similar over the sample collection period, including Cmax (111.8 [16.84] and 104.6 [18.07] µg/mL, respectively) and AUC(0-180days) (6134 [21.05] and 5874 [21.89] day*µg/mL, respectively. The observed PK profile of AZD8895 and AZD1061 were consistent with estimated AZD7442 half-life of 87.32 days.

There was a similar PK profile in subgroups based on CCI , although the sample size for the CCI is limited compared with the CCI (N = 12 and N = 190, respectively). There also a similar PK profile in subgroups based on COVID-19 vaccination status (vaccinated or not vaccinated at screening).

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. ADA prevalence (ADA positive at baseline and/or post-baseline) and incidence (TE-ADA positive) to AZD7442 was similar between the AZD7442 and placebo treatment groups (prevalence was 8.4% and 11.4%, respectively; incidence was 3.5% and 4.3%, respectively).

The median of maximum ADA titers to AZD8895 and AZD1061 in TE-ADA-positive participants in the AZD7442 arm were 160 and 320. respectively. The corresponding titers in TE-ADA-positive participants in the placebo arm were numerically similar at 160 and 160, respectively.

ADA had no apparent effect on AZD7442 PK.

There were no hypersensitivity events or CCI reactions in either the AD7442 or placebo groups reported during the study through the Primary Analysis DCO, nor were there any SAEs reported among ADA-positive participants treated with AZD7442. There was no apparent effect of ADA on the safety of AZD7442.

Summary of safety results

Up to the Primary Analysis DCO, a total of 38.6% and 40.0% participants had at least 1 AE in the AZD7442 and placebo groups, respectively. The majority of AEs were mild or moderate in intensity. There were no AEs leading to death in the study. Serious AEs were reported in by 1.5% and 1.4% participants in the AZD7442 and placebo groups, respectively. There were 2 AEs leading to dose interruption in the AZD7442 group, both of which resolved with participants receiving full or near-full doses of AZD7442.

There were no trends in AE profile related to vaccination status (vaccinated/not vaccinated at screening). There were no obvious trends observed in AEs by CCI although the small sample size in the older population (N = 16) limits the ability to draw conclusions.

In the AZD7442 group, the most common AE by PT (reported in > 5% of participants) was upper respiratory tract infection (reported by 7.9% and 7.1% of AZD7442 and placebo participants, respectively).

There were no AESIs (ie, hypersensitivity or CCI reactions) reported by the investigator in the study.

There were 2 participant in the AZD7442 group with COVID-19-related AEs (PTs: COVID-19 pneumonia and asymptomatic COVID-19).

There were no notable differences between the treatment groups in hematology, clinical chemistry, coagulation, or urinalysis. There were no apparent trends over time in hematology, clinical chemistry and coagulation values. There were more participants in AZD7442 group comparing to placebo group with shifts from normal to high in ALT (5.9% vs 1.4%), AST (4.5% vs 1.4%) and total bilurubin (4.5% vs 1.4%). The elevations were transient (most at a single time point only) and majority were within 2 times the upper limit of normal (ULN). None were ≥ 3 times the ULN (for ALT or AST) or ≥ 2 times the ULN (for total bilirubin). There were no instances of potential Hy's Law.

As of the Primary Analysis DCO, there were no notable differences between the treatment groups in vital signs, ECGs, physical findings, or other observations related to safety during the study.

Conclusion(s)

Up to the Primary Analysis DCO:

- Overall, a single dose of AZD7442 600 mg IV was well tolerated in healthy Chinese adults or those with a stable medical condition over a median follow-up duration of 238 days.
- Following IV infusion, serum concentrations of AZD8895 and AZD1061 rapidly achieved the maximum values CCI and thereafter slowly declined.
- For both component mAbs (AZD8895 and/or AZD1061) and AZD7442, the majority of ADA positive participants were not classified as TE-ADA positive. ADA prevalence and incidence to AZD7442 was similar between the treatment groups; the presence of ADA had no apparent effect on PK or safety.