Final Clinical Study Report	
Drug Substance	AZD7442
Study Code	D8850C00008
Edition Number	1
Date	05 October 2023
NCT Number	NCT05184062

A Phase II Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults

Final Report

Study dates: First participant enrolled: 03 December 2021
Last participant last visit: 06 May 2023
The Primary Analysis data cut-off was 15 August 2022
The analyses presented in this report are based on a final clinical data lock date of 14 July 2023

Phase of development: Therapeutic exploratory (II)

National Coordinating Investigator: PPD

Coordinating Principal Investigator PPD

Sponsor's Responsible Medical Officer: 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

This study was 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 [a]	
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	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 [b]	Where possible, PK parameters were assessed for individual mAbs (AZD8895 and AZD1061) [b]: • Cmax, AUC(0-180days) • Additional PK parameters that may be determined when appropriate include: ° AUClast, AUCinf, t1/2λz, tlast, Vss, Vz, and CL
To evaluate the ADA responses to AZD7442 in serum	Presence of ADA to AZD8895 and AZD1061 in serum [b] • Blood samples were collected and stored for analysis of ADAs. Unscheduled samples for ADA analysis may be collected in response to suspected immune-related AEs.

[a] The primary objective of safety and tolerability at 6 months after administration was assessed at the time of the primary clinical data lock. These results were reported in the primary clinical study report dated 23 November 2022 and are not included in this report.

[b] AZD8895 and AZD1061 are the 2 components of AZD7442.

Exploratory objectives and endpoints are not included in this Synopsis but are described in the body of the clinical study 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; ECG, electrocardiogram; IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics; SAE, serious adverse event; t1/2λz, 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

Study D8850C00008 was 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 CCI [redacted] at screening.

This study had 2 planned analysis points:

- Primary Analysis: After all treated participants completed (or withdrew from) follow-up through Day 181.
- Final Analysis: After all treated participants completed the study (ie, completed follow-up through Day 451) or withdrew from the study.

Investigators and participants remained blinded to the assigned study intervention until the end of the study. Selected personnel from the Sponsor were unblinded after the primary clinical data lock to perform the analysis for the report of the Primary Analysis (reported in the primary clinical study report, dated 23 November 2022).

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 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 Medicinal 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%

(weight per volume) 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

Data are presented by intervention groups (AZD7442 600 mg IV and placebo) using descriptive statistics. As appropriate, selected outputs are repeated by stratification factors age (> 60 years or ≤ 60 years) and COVID-19 vaccination status at screening (vaccinated or non-vaccinated).

The Primary Analysis was conducted after all treated participants completed follow-up through Day 181 or withdrew from the study. No early stopping decision was planned for futility or superiority at the Primary Analysis. The Final Analysis was conducted after all treated participants completed the study (ie, completed follow-up through Day 451) or withdrew from the study.

Primary Endpoint Analysis Methods (Safety at 6 Months Post-administration): The primary endpoint was assessment of safety at 6 months post-administration. Safety assessments, including AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), safety laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis); 12-lead electrocardiogram (ECG); vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were presented based on the Safety Analysis Set. The Safety Analysis Set was defined as all participants who received any amount of AZD7442 or placebo.

Secondary Endpoint Analysis Methods (Safety at 15 Months Post-administration): The analysis methods for the secondary endpoint of safety at 15 months post-administration were the same as the primary endpoint.

Secondary Endpoint Analysis Methods (Pharmacokinetics): Serum PK concentrations of each monoclonal antibody (mAb) (AZD8895 and AZD1061) and AZD7442 (ie, sum of AZD8895 and AZD1061) were listed and tabulated using descriptive statistics. Individual serum concentrations versus actual times grouped by mAb component were plotted on both linear and semi-logarithmic scales. Actual sampling time points relative to dosing were used for individual plots. Geometric means of concentration data were plotted over time on both linear and semi-logarithmic scales. Nominal sampling time points relative to dosing were used for mean plots. Pharmacokinetic analyses were based on the PK Analysis Set. The PK Analysis Set was defined as all participants in the Safety Analysis Set who received AZD7442

and had at least one quantifiable serum PK observation post-dose, with no important protocol deviations thought to impact the analysis of the PK data.

Secondary Endpoint Analysis Methods (Immunogenicity): The antidrug antibody (ADA) results to AZD8895, AZD1061 and AZD7442 were reported separately. In the evaluation of ADA results to AZD7442, if a component mAb (ie, AZD8895 or AZD1061) was not ADA evaluable, all results from the component would be treated as missing. For AZD1061, AZD8895 and AZD7442, the number and percentage of participants in each category of ADA responses were summarized descriptively by intervention group and study total based on the respective ADA Evaluable Analysis Sets. Summary statistics of maximum reported ADA titers were also presented in each category. The ADA Analysis Set was defined as all participants in the Safety Analysis Set who received any amount of AZD7442 or placebo and had a non-missing baseline ADA result and at least one non-missing post-baseline ADA result.

Study Population

A total of 726 participants were screened of whom 272 participants were randomized 3:1 to AZD7442 600 mg IV (N = 202 participants) or placebo (N = 70 participants) at 14 centers in China. All 272 participants were included in the Safety Analysis Set and the ADA Analysis Set. All 202 participants who received AZD7442 were included in the PK Analysis Set.

All 272 randomized participants completed the assigned study treatment of either AZD7442 or placebo. Overall, 265 (97.4%) randomized participants completed the study through to Day 451 follow-up. Only 7 (2.6%) randomized participants withdrew from the study. Five participants in the AZD7442 group and 1 participant in the placebo group were lost to follow-up; 1 participant in the AZD7442 group withdrew consent.

The study participants were representative of the target population for this study: healthy adults or adults with stable medical conditions in China, ≥ PPD of age. Participants who received study intervention (ie, AZD7442 or placebo) were Chinese adults, PPD years of age (mean 34.2 years), 69.1% were male, and 51.5% were COVID-19-vaccinated. Across the treatment groups, demographic and baseline characteristics were generally well balanced. There were no trends in participant disposition, important protocol deviations, pandemic-related study disruptions, or use of concomitant medications that would be expected to affect any study outcome or interpretation of results.

Summary of Pharmacokinetic Results

Following IV infusion of AZD7442, the PK properties were generally similar between the 2 component mAbs, AZD8895 and AZD1061. Maximum serum concentrations for AZD8895 and AZD1061 were achieved nearly immediately after IV infusion. The estimated half-life was approximately 80 to 84 days for AZD8895, AZD1061, and AZD7742. Clearance was

0.03806, 0.04061, and 0.03928 L/day for AZD8895, AZD1061, and AZD7442, respectively. Volume of distribution at steady state was 4.445, 4.536, and 4.490 L for AZD8895, AZD1061, and AZD7442, respectively. No age-related or COVID-19 vaccination status-related effects were observed on the exposure to AZD7442.

Summary of Immunogenicity Results

In the AZD7442 group, ADA prevalence of AZD7442 was 26.7%, and ADA incidence of AZD7442 was 20.8%. The ADA titers which resulted from AZD7442 administration were similar to those which resulted from placebo administration. The presence of ADA had no apparent effect on the PK or safety of AZD7442.

Summary of Safety Results

A total of 72.8% and 80.0% participants had at least one AE in the AZD7442 and placebo groups, respectively. The majority of AEs were mild or moderate in intensity. There were no clinically significant trends in AE safety profile related to CCI or COVID-19 vaccination status at screening (vaccinated/non-vaccinated).

There were no AEs leading to death in the study.

Serious AEs were reported in 3.0% and 4.3% participants in the AZD7442 and placebo groups, respectively. All SAEs were assessed as not IMP-related by investigators.

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, and both were considered by the investigator as related to the study procedure and not to the IMP.

In the AZD7442 group, the most common AEs by preferred term (reported in > 5% of participants) were COVID-19 (28.7% and 28.6% of AZD7442 and placebo participants, respectively), upper respiratory tract infection (14.4% and 18.6% of AZD7442 and placebo participants, respectively), influenza like illness (9.9% and 5.7% of AZD7442 and placebo participants, respectively), protein urine present (7.4% and 8.6% of AZD7442 and placebo participants, respectively), and suspected COVID-19 (5.9% and 20.0% of AZD7442 and placebo participants, respectively).

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

COVID-19-related AEs were reported in 71 (35.1%) participants in the AZD7442 group and in 34 (48.6%) participants in the placebo group. For the majority of participants with COVID-19-related AEs (103 of 105 participants), the onset date of the first COVID-19-related AE was late in the study (with onset dates from Day 278 onwards).

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

Overall, a single dose of AZD7442 600 mg IV was well tolerated in healthy Chinese adults or those with a stable medical condition with a median duration follow-up of 447 days, including in participants > 60 years of age and in those with prior COVID-19 vaccination.

Conclusions

- Overall, a single dose of AZD7442 600 mg IV was well tolerated in adult Chinese participants over a median follow-up duration of 447 days.
- Following IV infusion of AZD7442, the PK properties were generally similar between the 2 component mAbs, AZD8895 and AZD1061.
  - Maximum serum concentrations for AZD8895 and AZD1061 were achieved nearly immediately after IV infusion.
  - The estimated half-life was approximately 80 to 84 days for AZD8895, AZD1061, and AZD7742.
  - Clearance was 0.03806, 0.04061, and 0.03928 L/day for AZD8895, AZD1061, and AZD7442, respectively.
  - Volume of distribution at steady state was 4.445, 4.536, and 4.490 L for AZD8895, AZD1061, and AZD7442, respectively.
- Overall median ADA titers against AZD7442 (combined responses) in treatment-emergent-ADA-positive participants were numerically similar for AZD7442 and placebo groups. The presence of ADA had no apparent effect on PK or safety.