2. SYNOPSIS

Study Center

A total of 60 healthy participants were enrolled at a single study center.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Measurements

Objectives	Outcome Measures
Primary	
• To evaluate the safety and tolerability of AZD7442 administered CCI or CCI to healthy adult participants 18 to 55 years of age	• AEs, SAEs, safety laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis); 12-lead safety ECG; vital signs (BP, pulse rate, oral temperature, and respiratory rate), and physical examination • Injection site reactions were monitored for the CCI injection cohort (including assessment of size, redness/erythema, swelling, itching/pruritis, pain or tenderness, induration, discoloration) and was recorded as an AE and a photograph taken, at the discretion of the PI, with visible measuring tape
Secondary	
• To evaluate the single dose PK of AZD7442 (when mAbs are administered sequentially [divided in separate infusion of each mAb component], and when mAbs are co-administered [both mAbs mixed into a single infusion]) in serum	• After CCI infusion: C_{max}, t_{max}, $t_{½\lambda z}$, AUC_{last}, AUC_{inf}, V_{ss}, V_z, and CL • After CCI injection: C_{max}, t_{max}, $t_{½\lambda z}$, AUC_{last}, AUC_{inf}, extravascular CL/F, F, and extravascular V_z/F
• To evaluate the ADA responses to the AZD7442 in serum	• Incidence of ADA to AZD7442 in serum over time
Exploratory	
• CCI	• CCI
• CCI	• CCI

ADA, antidrug antibody; AE, adverse event; AUC_{inf}, area under the serum concentration versus time curve extrapolated to infinity; AUC_{last}, area under the serum concentration versus time curve from time zero to time of last measurable concentration; BP, blood pressure; CL, systemic clearance; CL/F, apparent total clearance; C_{max}, maximum serum concentration; ECG, electrocardiogram; F, bioavailability; IM, intramuscular; IV, intravenous; mAbs, monoclonal antibodies; PI, principal investigator; PK, pharmacokinetics; $t_{½\lambda z}$, terminal elimination half-life; t_{max}, time to maximum serum concentration; SAEs, serious adverse events; CCI; V_{ss}, volume of distribution at steady state; V_z, volume of distribution at terminal phase; V_z/F, apparent volume of distribution at terminal phase.

Study Design

This was a Phase I, first-time-in-human, randomized, double-blind, placebo-controlled, dose escalation study evaluating the safety, tolerability, and pharmacokinetics (PK) of AZD7442 in healthy adult participants between 18 and 55 years of age. AZD7442 is a combination product of 2 monoclonal antibodies (mAbs), AZD8895 and AZD1061. 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 CCI = AZD8895 CCI + AZD1061 CCI.

All participants were enrolled at one study center and randomized 10:2 to either AZD7442 or placebo administered CCI or CCI across 5 fixed-dose cohorts:

- Cohort 1a: participants received CCI of AZD7442 or placebo via CCI administered in 2 sequential gluteal CCI injections starting with CCI AZD8895/placebo and followed by CCI AZD1061/placebo.
- Cohort 1b: participants received CCI AZD7442/placebo via CCI infusion administered in 2 sequential CCI infusions at a maximal infusion rate of CCI, starting with CCI AZD8895/placebo and followed by CCI AZD1061/placebo.
- Cohort 2: participants received CCI AZD7442/placebo via CCI infusion administered in 2 sequential CCI infusions at a maximal infusion rate of CCI, starting with CCI AZD8895/placebo and followed by CCI AZD1061/placebo.
- Cohort 3: participants received CCI AZD7442/placebo via CCI administered in 2 sequential CCI infusions at a maximal infusion rate of CCI, starting with CCI AZD8895/placebo and followed by CCI AZD1061/placebo.
- Cohort 4: participants received CCI AZD7442/placebo via CCI infusion, the IMP was co-administered as a single CCI infusion containing both mAbs (CCI of AZD8895 and CCI of AZD1061)/placebo at a maximal infusion rate of CCI.

After dosing, participants were monitored for one year (Day 361) for safety, including recording of adverse events (AEs), serious adverse events (SAEs), and collection of blood samples for PK and antidrug antibodies (ADAs).

Target Population and Sample Size

This study was conducted in 60 healthy male and female participants, 18 to 55 years of age. Because all analyses were descriptive in nature and no hypothesis was tested statistically, no formal sample size calculations were performed. However, the sample size was considered sufficient for an early assessment of safety, tolerability, immunogenicity, and PK.

Investigational Product and Placebo: Dosage, Mode of Administration, and Batch Numbers

At randomization, participants were randomly assigned to one of 2 treatments. Each participant in this study received a single dose of either placebo or AZD7442.

- AZD7442: (combined doses of AZD8895 and AZD1061 each representing half of the total dose) were manufactured by AstraZeneca. The doses were administered sequentially for Cohorts 1a, 1b, 2, and 3 (CCI CCI, CCI CCI, CCI CCI, and CCI CCI, respectively) at CCI for the CCI infusions; or co-administered for Cohort 4 (CCI CCI infusion at CCI CCI).
  - AZD8895 CCI LYO P1 10R 1 vial/kit, Batch: CCI
  - AZD1061 CCI LYO P1 10R 1 vial/kit, Batch: CCI
- Placebo: participants randomized to placebo received the same volume of placebo solution as participants on AZD7442 treatment. Placebo was supplied by the Clinical Unit.

Duration of Treatment

This was a single dose study carried out over approximately 389 days for each participant, consisting of a Screening Period of up to 27 days (Day -28 through Day -2), a Treatment Period of 2 days (Day -1 to Day 1 with IMP administered on Day 1), and a 360-day safety Follow-up Period (Day 2 through Day 361).

Statistical Methods

All original and derived parameters, as well as demographic and disposition data, were listed and described using summary statistics. All safety data (scheduled and unscheduled) were presented in the data listings.

Demographic and baseline data were summarized by treatment group (dose level or administration process of AZD7442, total AZD7442, and pooled placebo). Pharmacokinetic data were summarized by treatment group. Available safety and tolerability data were summarized by treatment group (dose level or administration process of AZD7442, total AZD7442, and pooled placebo).

Frequency counts (number of participants [n] and percentages) were made for each qualitative variable. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were calculated for each quantitative variable (unless otherwise stated). Descriptive statistics was only presented if $n > 3$. If no participants had data at a given time point, then only $n = 0$ was to be presented. If $n < 3$, only the n, minimum and maximum were presented, and if $n = 3$, only the n, median, minimum, and maximum were presented; the other descriptive statistics were left blank.

Study Population

Overall, 253 participants were screened (all participants signed the ICF), of which 60 participants were enrolled in this study. A total of 10 participants were enrolled and randomized to AZD7442 in each cohort, and 10 participants were randomized to pooled placebo.

Summary of Serum Pharmacokinetic Results

After a single CCI CCI dose, the geometric mean maximum serum concentration (C_{max}) was similar for AZD8895 and AZD1061 at 16.52 and 15.27 µg/mL, respectively, which was reached at a median time to maximum serum concentration of approximately 14 days for both antibodies. Between-participant variability (percent coefficient of variation [%CV]) in AZD8895 area under the curve (AUC_{inf}) and C_{max} after CCI CCI administration was 29.75% and 35.56%, respectively, and 31.25% and 38.53%, respectively, for AZD1061. The PK of AZD8895 and AZD1061 up to Day 361 were similar. The bioavailability of AZD7441 administered by CCI at CCI calculated as the ratio of geometric mean AUC_{inf} after CCI to CCI, was 68.69% and 65.02% for AZD8895 and AZD1061, respectively.

After CCI CCI administration, between-participant variability (%CV) in AZD8895 AUC_{inf} and C_{max} was 13.75% and 10.24%, respectively, and 14.17% and 12.31%, respectively, for AZD1061.

After CCI CCI administration, between-participant variability (%CV) in AZD8895 AUC_{inf} and C_{max} was 12.58% and 11.31%, respectively, and 11.69% and 14.66%, respectively, for AZD1061.

After CCI CCI administration, administered as CCI of AZD8895 over 75 minutes followed by CCI of AZD1061 over another 75 minutes (Cohort 3), the between-participant variability (%CV) in AZD8895 AUC_{inf} and C_{max} was 10.85% and 10.54%, respectively, and 11.71% and 11.09%, respectively, for AZD1061. After 3000 mg CCI administration, with CCI of AZD8895 and CCI of AZD1061 administered at the same time over 60 minutes (Cohort 4), the between-participant variability (%CV) in AZD8895 AUC_{inf} and C_{max} was 11.89% and 8.980%, respectively, and 11.82% and 11.62%, respectively, for AZD1061.

Overall, the C_{max} and AUC increased linearly with increasing IV dose. Administering AZD8895 and AZD1061 separately or together did not alter the PK of the mAbs as indicated by the nearly identical serum drug concentration-time curves for the two CCI CCI dosing regimens. In addition, key exposure PK parameters such as AUC and C_{max} for AZD8895 and AZD1061 were similar for those dosing regimens.

The mean $t_{1/2\lambda z}$ calculated for both antibodies from all cohorts was 88.33 days, ranging from 86.97 to 95.33 days for AZD8895 and 79.78 to 91.08 days for AZD1061.

Summary of Immunogenicity

At the time of final analysis, all 60 participants in the study (50 of whom received AZD7442 and 10 placebo) had a non-missing baseline and at least 1 non-missing post baseline ADA result.

One out of 50 participants in the AZD7442 cohorts tested positive for ADA to AZD8895. The participant was in Cohort 1a (CCI CCI), and had a positive ADA result at Day 361 only and negative results at all other assessments. The ADA titer was low, at the limit of detection of 80. Seven out of 50 participants in the AZD7442 cohorts tested positive for ADA to AZD1061, 4 in Cohort 1a (CCI CCI) and 3 in Cohort 1b (CCI CCI), including the participant who was ADA-positive to AZD8895. All 7 participants had a positive ADA result at Day 361 only and negative results at all other assessments. All ADA titers were low, either reported as borderline positive (≤ 40) or close to the limit of detection of 40. No participants who received placebo were ADA-positive.

Overall, 7 out of 50 participants were ADA-positive to AZD7442 (defined as having a positive result to AZD8895 and/or AZD1061) in the study. All 7 participants had a positive ADA result at Day 361 only and negative results at all other assessments; ADA titers were consistently low across all 7 participants.

Summary of Safety Results

The safety and tolerability data over the whole study period (361 days) did not raise any safety concerns in any of the cohorts.

A total of 26 (52.0%) participants receiving AZD7442 reported at least one AE.

- Cohort 1a (AZD7442 CCI CCI) 2 (20%) participants reported 3 AEs.
- Cohort 1b (AZD7442 CCI CCI) 5 (50%) participants reported 15 AEs.
- Cohort 2 (AZD7442 CCI CCI) 6 (60%) participants reported 14 AEs.
- Cohort 3 (AZD7442 CCI CCI) 7 (70%) participants reported 16 AEs.
- Cohort 4 (AZD7442 CCI CCI co-administered) 6 (60%) participants reported 10 AEs.

In total, 8 (80%) participants in the pooled placebo group reported 14 AEs.

Overall, there were no clinically meaningful imbalances in AEs across treatment groups. All AEs reported (72) were either mild (52) or moderate (20) in intensity; there were no AEs of severe intensity. The number of participants with AEs that were possibly related to the IMP were similar between the total AZD7442 group (8 [16%] participants) and the pooled placebo group (2 [20%] participants). The AEs had no impact on PK.

There were no deaths or SAEs, or AEs resulting in discontinuation of IMP in any participant. There was one case of dose interruption due to an AE and 2 other infusion interruptions due to an air bubble and air in the infusion line.

There were no apparent clinically meaningful differences between treatment groups in mean hematology or clinical chemistry parameters over time, or in shifts from normal to high/low in individual parameters.

There were no apparent clinically meaningful differences between treatment groups in mean vital signs or ECG parameters.

Conclusions

- No tolerability or safety signals were observed in this healthy adult population. These results demonstrated an acceptable safety profile for AZD7442, including no observed infusion-related reactions (for CCI administration), injection site reactions (for IM administration), or hypersensitivity reactions.
- The estimated $t_{1/2\lambda z}$ of AZD8895 and AZD1061 were similar and comparable between dose cohorts. The mean terminal $t_{1/2\lambda z}$ was approximately 90 days.
- The PK of AZD8895 and AZD1061 up to Day 361 are similar. Sequential and co-administration of AZD8895 and AZD1061 does not alter the PK profile.
- The bioavailability of AZD7442 administered by CCI at CCI calculated as the ratio of geometric mean AUCinf after CCI to CCI, was 68.69% and 65.02% for AZD8895 and AZD1061, respectively.
- Overall, 7 out of 50 participants in the AZD7442 cohorts tested positive for ADA to either AZD8895 or AZD1061; 1 participant was ADA-positive to both mAbs. No participants who received placebo were ADA-positive. ADA titers to AZD8895 or AZD1061 were low.
- CCI
- CCI