A Randomised, Single-blind, Single-centre, Placebo-controlled, Phase I Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD7503 Following Multiple Subcutaneous Dose Administration in Healthy Japanese Participants

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Clinical Study Report Synopsis	
Drug Substance	AZD7503
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Study Dates:	First participant screened: 25 October 2023 Last participant last visit: 20 March 2024
Phase of Development:	Clinical pharmacology (I)
Study Sponsor:	AstraZeneca K.K.

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

Study Site

The study was performed at a single study site in Japan.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of AZD7503 following SC administration of multiple doses in healthy Japanese participants.	Safety and tolerability were evaluated in terms of: • AEs and SAEs. • 12-lead safety ECGs, dECGs, and telemetry. • Vital signs (including BP, pulse rate, and body temperature). • Physical examination. • ISRs. • Clinical laboratory evaluations (haematology, including platelet count, clinical chemistry, and coagulation, renal safety biomarkers, immune activation response, complement activation panel, and urinalysis).
Secondary	
• To characterise the PK of AZD7503 in plasma and urine following SC administration of multiple doses in healthy Japanese participants.	• Evaluation of AZD7503 full-length oligonucleotide concentrations and standard PK parameters (including but not limited to Cmax, AUClast, AUCinf, and AUCtau) and urine PK parameters (Ae and Fe). • Evaluation of plasma concentrations of AZD7503 and unconjugated ASO at specified timepoints.

For exploratory objectives and endpoints, please refer to the body of the Clinical Study Report.

Ae, amount of analyte excreted into the urine; AEs, adverse events; ASO, antisense oligonucleotide; AUCinf, area under plasma concentration-time curve from time 0 to infinity; AUClast, area under the plasma concentration-time curve from time) to last quantifiable concentration; AUCtau, area under plasma concentration-time curve during a dosing interval; BP, blood pressure; Cmax, maximum observed plasma drug concentration; dECGs, digital electrocardiograms; ECGs, electrocardiograms; Fe, fraction of the dose excreted unchanged in urine; ISRs, injection site reactions; PK, pharmacokinetic(s); SAEs, serious adverse events; SC, subcutaneous.

Study Design

This Phase I, randomised, single-blind, placebo-controlled study was designed to assess the safety, tolerability, and pharmacokinetics (PK) of AZD7503 following multiple subcutaneous (SC) doses in healthy Japanese participants.

The study comprised of:

- A Screening Period of maximum 28 days.
- Randomisation on Day 1.
- A 9-week Treatment Period, during which participants were residents at the study site for Dose 1 and Dose 3.
  - Dose 1 was administered on Day 1 at the study site and participants resided at the study site from Day -1 until at least 2 days after the study intervention administration with discharge on Day 3.
  - Dose 2 was administered at the study site on Day 29 with no overnight stay.
  - Dose 3 was administered on Day 57 and participants resided at the study site from Day 56 until at least 2 days after study intervention administration with discharge on Day 59. Study intervention was administered after a 10-hour fast.
- A Follow-up Period of 10 weeks post last dose of study intervention, that consisted of 3 Follow-up Visits (including Final/Early Termination Visit), for which the participants returned to the study site at Weeks 11, 13, and 19.

The Safety Review Committee (SRC) would have reviewed safety and tolerability data (adverse events [AEs] and serious adverse events [SAEs], vital signs [blood pressure (BP), pulse rate, and body temperature], 12-lead safety electrocardiograms [ECGs], digital ECGs [dECGs], telemetry, physical examination, injection site reactions [ISRs], laboratory assessments [haematology, clinical chemistry, coagulation, renal safety biomarkers, immune activation response, complement activation panel, and urinalysis]), and available PK data collected up to 2 weeks after the last dose to decide if a second cohort was needed. However, AstraZeneca made the decision not to proceed to Cohort 2 as the development of AZD7503 was put on hold (the SRC did not meet).

Target Population and Sample Size

This study was to be conducted in up to 24 healthy male and female participants of non-childbearing potential, aged 18 to 60 years of age. Participants had to be of Japanese ethnicity, defined as having both parents and 4 grandparents who were ethnically Japanese (this included second and third generation Japanese whose parents or grandparents were living in a country other than Japan). Participants must have had a body mass index between 18 and 32 kg/m^2, inclusive and weighed at least 50 kg. Participants had to be willing to provide [redacted]

Due to the exploratory nature of the study, the sample size was not based on formal statistical considerations. The sample size was based on experience from similar Phase I studies

previously conducted with AZD7503 and other compounds. The initial cohort had 12 participants who were randomly assigned in a 3:1 ratio to receive AZD7503 or placebo. Nine participants were randomised to receive AZD7503, and 3 participants were randomised to receive placebo with an aim to have 7 participants on AZD7503 and 2 participants on placebo completing the study.

Investigational Product and Comparator: Dosage, Mode of Administration

AZD7503, solution for injection, provided in single dose vials, was administered via SC injection at CCI mg/mL.

Placebo, CCI% saline solution (sodium chloride) for injection, provided in single dose vial, was administered via SC injection at a matching volume to AZD7503.

Duration of Treatment

The treatment duration was up to 9 weeks, including 3 SC injections 4 weeks apart (Visit 2, Visit 4, and Visit 6).

Statistical Methods

This Phase I study was designed to assess safety, tolerability, and PK without formal hypothesis testing. As such, there was no adjustment for multiplicity. No statistical hypotheses were planned to be tested in this study and only descriptive statistics were presented.

All statistical analyses were performed using Statistical Analysis Software 9.4.

Safety and tolerability were evaluated in terms of AEs/SAEs, vital signs (BP, pulse rate, and body temperature); 12-lead safety ECG, dECG, and telemetry, physical examination, ISRs, laboratory assessments (haematology including platelet count, clinical chemistry, coagulation, renal safety biomarkers, immune activation response, complement activation panel, and urinalysis). Safety data were summarised descriptively and were not formally tested.

Continuous variables were summarised using descriptive statistics by treatment and overall, as appropriate. Shifts from baseline levels that were measured at screening and the last pre-dose, were reviewed in addition to data that were outside reference range.

Categorical variables were summarised in frequency tables (frequency and proportion) by treatment and overall, as appropriate. The analysis of the safety variables was based on the Safety Analysis Set.

PK analysis was conducted based on the plasma concentrations of AZD7503 full-length oligonucleotide, AZD7503, and unconjugated AZD7503 and urine concentrations of AZD7503.

Where data allowed, PK parameters were calculated for plasma AZD7503 full-length oligonucleotide, and urine AZD7503 and unconjugated AZD7503, using non-compartmental analyses, using actual elapsed sampling times and standard non-compartmental methods.

All PK concentrations and any derived PK parameters were listed and summarised. The PK concentrations and parameter listings were presented for the PK Analysis Set. Plasma concentrations and PK parameters were summarised and presented using appropriate descriptive statistics for the PK Analysis Set.

Study Population

- The randomised healthy Japanese participants were representative of the population to be evaluated in this study, although no females were included.
- The demographic and key baseline characteristics were generally well balanced between the AZD7503 and placebo treatment groups and any differences were not considered likely to influence the results of the study.
- None of the other baseline assessments, eg, medical and surgical history and use of concomitant medications were considered likely to affect the outcome of the study.

Summary of Safety Results

- Whilst most participants in the AZD7503 group reported at least one AE (77.8%), there were no deaths or SAEs, and only one participant had an AE that led to discontinuation of study intervention. No AEs were reported in the placebo group.
- The AEs reported were generally as expected per the known risks and safety profile of AZD7503.
  - AEs reported for increases in liver transaminases were mild and non-serious (Alanine aminotransferase increased in 4 [44.4%] participants, Aspartate aminotransferase increased in 2 [22.2%] participants).
  - ISR AEs were reported in one (11.1%) participant.
- No clinically important trends were observed for 12-lead safety ECGs, dECGs, telemetry, vital signs, and physical examinations.
- No clinically important trends were observed for clinical laboratory evaluations (haematology, including platelet count, clinical chemistry, and coagulation, renal safety biomarkers, immune activation response, complement activation panel, and urinalysis). Whilst there were AEs reported for increases in liver transaminases these were mild and non-serious and were as expected per the safety profile of AZD7503 and N-acetylgalactosamine-conjugated antisense oligonucleotides.
- AZD7503 was well tolerated following SC administration of multiple doses in healthy Japanese participants.

Summary of Pharmacokinetic and CCI Results

- AZD7503 was rapidly absorbed with median tmax occurring at 2.02 h post-dose on Day 1 and 1.77 h post-dose on Day 57, followed by a biphasic decline in concentrations.
- The terminal phase was characterised by a long half-life, with a geometric mean terminal elimination half-life of 243.5 h on Day 1 and 417.6 h on Day 57.
- No evidence of accumulation or time dependent PK following multiple doses with geometric mean temporal change parameter and accumulation ratios close to 1.
- Moderate to high between participant variability (based on geometric coefficient of variation percentage) in exposure.
- Low urinary excretion, with less than 2.42% of dose being excreted as AZD7503.
- CCI

Summary of Efficacy Results

Not applicable for this study.

Conclusions

- AZD7503 was well tolerated following SC administration of multiple doses in healthy Japanese participants.
- The PK of AZD7503 was characterised by rapid absorption followed by extensive distribution and a long terminal elimination phase, no evidence of accumulation or time dependent PK following multiple doses and negligible urinary excretion.
- CCI