2 SYNOPSIS

Title of Study:	A Phase I, First-in-Human, Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2373 following Single Ascending Dose Administrations to Healthy Male Subjects of African Ancestry	
Study Numbers:	Parexel Study No.: 245956 Sponsor Study No.: D6800C00001	
Investigational Medicinal Products:	Test Product: AZD2373 Reference Product: Placebo	
Indication Studied:	Chronic Kidney Disease	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Dr Ronald Goldwater, MD	
Study Center:	Parexel Early Phase Clinical Unit - Baltimore	
Publication:	None	
Study Duration:	First subject first visit: 13 February 2020	Last subject last visit: 31 August 2021

Study Objectives:

Primary objective:

- To investigate the safety and tolerability of subcutaneous (SC) single ascending dose (SAD) administrations of AZD2373.

Secondary objectives:

- To characterize the pharmacokinetics (PK) of AZD2373 following SC SAD administrations of AZD2373.
- To assess the effect of SC SAD administrations of AZD2373 on plasma concentrations of apolipoprotein L1 (APOL1) protein.

Result for exploratory objectives will not be reported in the clinical study report (CSR).

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Study Design:

This study was randomized, single-blind, placebo-controlled, SAD sequential group study in healthy male subjects of West African ancestry performed at a single study center.

The study was planned to include 6 single dose cohorts with the option to include 2 additional cohorts. However, the study included 4 single dose cohorts. Provisional doses of AZD2373 were CCI and CC mg, however, actual doses given in the study were CCI mg. Dose escalation was stopped after the CC mg dose.

The study comprised of:

- A Screening Period of maximum 35 days,
- A Treatment Period during which subjects were resident at the Clinical Unit from the day before investigational medicinal product (IMP) administration (Day -1) until at least 72 hours after IMP administration; discharged from the Clinical Unit on Day 4,
- Follow-up Visits on 1, 1.5, 2, 3, 4, 5, 6, and 8 weeks (Visits 3 to 10), and
- A Final Follow-up Visit 10 weeks after the last IMP dose.

Safety data collected during dosing and up to 3 weeks post-dose, as well as PK and pharmacodynamics (PD) collected during dosing and up to 1 week (Cohorts 1 to 3) or 2 weeks (Cohort 4) post-dose would be the basis for decisions on the dose level for the cohorts; these data were reviewed by a Safety Review Committee (SRC).

Study Subjects:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
Approximately 48 subjects	31 subjects	30 subjects

Main Inclusion Criteria:

Healthy male subjects of West African ancestry aged 18 to 55 years (inclusive) with suitable veins for cannulation or repeated venipuncture. Subjects had to have a body mass index (BMI) between 18 and 35 kg/m^2, inclusive and weigh at least 50 kg and no more than 120 kg, inclusive. The definition of West African ancestry was that: both the subject's biological parents and all four grandparents were believed to be West African or of West African descent, as confirmed by interview. Unless known to have other origins, African Americans or Afro Caribbeans could be assumed to have West African ancestry.

Investigational Medicinal Product(s):

Formulations:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Numbers:**	**Expiry Dates:**
AZD2373 (solution for injection)	CCI mg/mL	P Lot ID: CCI F Lot ID: CCI	31 Aug 2021 per batch certificate for release of packaged IMP (document date 09 Feb 2021)
Placebo (saline solution for injection)	0.9% sodium chloride	CCI CCI	01 Mar 2021 (1st shipment) 01 Jan 2022 (2nd shipment)

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Duration of Treatment:

Each subject was to be involved in the study for up to 10 weeks (excluding an up to 35-day Screening Period).

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit in Baltimore. The administration of all IMPs was recorded in Parexel's electronic source data capturing and information management system (ClinBase™). Compliance was assured by direct supervision and witnessing of IMP administration.

Criteria for Evaluation:

Safety Variables:

Primary safety parameters:

- Adverse events (AEs).
- Vital signs (supine blood pressure [BP], pulse, and temperature).
- Electrocardiography (paper and digital 12-lead electrocardiograms [ECGs] [pECG; dECG]), and telemetry monitoring.
- Physical examination.
- Injection site reaction examination.
- Laboratory assessments (hematology, clinical chemistry, coagulation, platelet count, complement activation panel, high density lipoproteins [HDL], renal safety biomarkers, serum total bile acids, and urinalysis).

Pharmacokinetic Parameters:

Secondary PK parameters: AUCinf, AUClast, AUC(0-72), AUC(0-48), Cmax, tmax, t½λz, CL/F, Vz/F, MRTinf, λz, tlast, Ae(0-last), fe(0-last), Ae(t1-t2), fe(t1-t2), and CLR.

Pharmacodynamic Variables:

APOL1 protein concentrations and change from baseline in APOL1 protein concentrations were assessed.

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Statistical Methods:

Determination of Sample Size:

This was a Phase I study to investigate the safety and tolerability of a novel compound. The sample size of 48 subjects (to ensure at least 42 evaluable subjects at the end of the last treatment period) was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of subjects to the compound at this phase of clinical development. Previous experience in Phase I studies had shown that the sample size being proposed was reasonable to accomplish the objectives of the study.

Presentation and Analysis of Pharmacokinetic Data:

The PK analysis set consisted of all subjects in the safety analysis set who received AZD2373 and who had evaluable PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

The exclusion of any subjects or time points from the calculation of the PK parameters was documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set were listed only. Concentration data for subjects excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

Presentation and Analysis of Safety Data:

All subjects who received at least 1 dose of IMP were included in the safety analysis for the study.

Unless otherwise stated the safety analysis set was used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP was also presented using the safety analysis set.

Presentation and Analysis of Pharmacodynamic Data:

The PD analysis set consisted of all subjects in the safety analysis set, who had at least the baseline (Day 1, pre-dose) and one post-dose measurement of APOL1 protein plasma concentration, and who had no important protocol deviations thought to impact on the analysis of the PD data.

The available PD data for any subjects excluded from the PD analysis set were listed only. Only subjects in the PD analysis set were included in the descriptive summary tables.

Protocol Deviations:

No protocol deviations were reported.

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Pharmacokinetic and Pharmacodynamic Results:

- AZD2373 was rapidly absorbed following SC administration with a median tmax of 2.00 to 3.00 hours.
- Geometric mean CL/F was comparable across all doses.
- Geometric mean renal clearance appeared to increase with increasing doses, but renal elimination was negligible.
- AUCinf, AUC(0-last), AUC(0-48), AUC(0-72), and Cmax for AZD2373 increased in a dose proportional manner.
- AZD2373 t½λz appeared to increase with increasing doses but was likely due to more robust capture of the terminal phase at higher dose levels.
- Inter-subject variability (based upon geometric CV%) was generally low (< 25%) to moderate (25% to 40%) for AUCinf, AUC(0-last), AUC(0-48), AUC(0-72), and Cmax.
- There was a trend for decrease in plasma APOL1 from baseline following a single dose in active treatment groups that was not observed in the placebo group. Geometric mean reductions greater than 20% from baseline was observed at selected time points. However, no clear dose-response was observed in the data.

Safety Results:

- No safety concerns were identified in this study up to the highest dose given CCI mg). Pre-defined study stopping criteria were not reached.
- No serious adverse events (SAEs) or deaths were reported in the study. There was no discontinuation of the study in the AZD2373 group.
- Overall, 11 subjects experienced at least 1 TEAE. Treatment emergent adverse events reported in the study were mild or moderate.
- Delayed and persistent, mild to moderate ISRs were reported after administration of CCI mg and CCI mg AZD2373. The most frequently reported ISRs were discoloration, color (redness/erythema), swelling, and itching.
- Vital signs, 12-lead ECGs, and safety laboratory data did not show any clinically significant, time- or dose-dependent effect. Two subjects (one subject in the placebo group and one subject in the CCI mg AZD2373 group) reported non-sustained ventricular tachycardia.
- Change from baseline across all treatment groups for the CCI biomarkers was comparable to the placebo group.

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Discussion and Conclusion:

Discussion:

The study assessed the safety and tolerability of SC SAD administration of AZD2373. The study results showed that there were no new safety signals observed when AZD2373 (up to CCI mg) was administered as single doses in male subjects of African Ancestry.

There were no concomitant medications, AEs, or protocol deviations considered to impact PK parameter estimation. AZD2373 exposure increased proportional to the increase in dose across the evaluated dose range. The apparent increase in t½λz with increasing doses was likely due to more robust terminal phase capture at higher dose levels.

There was a trend for decrease in plasma APOL1 from baseline following a single dose in active treatment groups that was not observed in the placebo group. Geometric mean reductions greater than 20% from baseline was observed at selected time points. However, no clear dose-response was observed in the data.

The results demonstrated an acceptable safety profile, and the IMP was well tolerated in the studied population.

Conclusion:

- No safety concerns were identified in this study up to the highest dose given (CCI mg). Pre-defined study stopping criteria were not reached.
- No SAEs or deaths were reported in the study. There was no discontinuation of the study in the AZD2373 group.
- Overall, 11 subjects experienced at least 1 TEAE. Treatment emergent adverse events reported in the study were mild or moderate.
- Delayed and persistent, mild to moderate ISRs were reported after administration of CCI mg and CCI mg AZD2373. The most frequently reported ISRs were discoloration, color (redness/erythema), swelling, and itching.
- Vital signs, 12-lead ECGs, and safety laboratory data did not show any clinically significant, time- or dose-dependent effect. Two subjects (one subject in the placebo group and one subject in the CCI mg AZD2373 group) reported non-sustained ventricular tachycardia.
- Change from baseline across all treatment groups for the CCI biomarkers was comparable to the placebo group.
- AZD2373 was rapidly absorbed following SC administration and exposure increased in a dose proportional manner across the evaluated single dose range. Geometric mean CL/F was comparable across all doses. Geometric mean renal clearance appeared to increase with increasing doses, but renal elimination was negligible. t½λz appeared to increase with increasing doses, likely due to more robust capture of the terminal phase at higher dose levels.
- There was a trend for decrease in plasma APOL1 from baseline following single dose in active treatment groups that was not observed in the placebo group. However, no clear dose-response was observed in the data.

Version and Date of Report: Version 1, 26 July 2022

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.