2 SYNOPSIS

Title of Study:	A Phase I randomized, single-blind, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of AZD5462 following single and multiple ascending dose administration to healthy volunteers	
Study Numbers:	Parexel Study No.: Pxl 258426 Sponsor Study No.: D9090C00001	
Investigational Products:	Study drug: AZD5462 Reference Product: Placebo	
Indication Studied:	Heart Failure	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit – Los Angeles	
Publication:	None	
Study Duration:	First participant first visit: 27 Jul 2021	Last participant last visit: 20 Sep 2022

Study Objectives:

Primary objective (Part A and Part B):

- To assess the safety and tolerability of AZD5462 following oral administration of single ascending doses (SAD) (Part A) and multiple ascending doses (MAD) (Part B).

Secondary objective (Part A and Part B):

- To characterize the single dose and steady state pharmacokinetics (PK) of AZD5462 following oral administration.

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CCI [redacted]

Study Design:

This study was a Phase I, First-in-Human (FIH), randomized single-blind, placebo-controlled study to assess the safety, tolerability, and PK of AZD5462 following SAD and MAD administration in healthy male and female (of non-childbearing potential) participants and healthy participants of Japanese descent (JD), performed at a single study center. It consisted of 2 parts (Part A and Part B) with an interleaved study design.

Part A (SAD Study)

Part A of the study was a sequential SAD design with 5 dose levels planned to be investigated across 8 cohorts, of which 3 cohorts comprised solely of participants of JD. One planned cohort was canceled (Cohort 8, 1000 mg JD) and was not dosed because the PK data from preceding cohorts suggested that the systemic exposure limits defined in the study protocol might be exceeded. Therefore, only 7 cohorts were dosed. Overall, it was planned that 64 healthy participants would participate across the 8 original cohorts, with 8 participants in each cohort. Within each cohort, 6 participants were randomized to receive AZD5462, and 2 participants randomized to receive placebo.

On Day 1, a single dose of AZD5462 or placebo was administered to each participant. Dosing for each ascending dose cohort was proceeded with 2 participants in a sentinel sub-cohort. The safety data for the sentinel participants for at least 24 hours post-dose (approximately 5 times the predicted plasma half-life) were reviewed by the Principal Investigator (PI) before the remaining participants in the cohort were dosed. Participants remained at the clinic from Day -4 until Day 3.

Part B (MAD Study)

Part B of the study was a sequential MAD design with 4 dose levels of AZD5462 investigated across 5 cohorts, of which 1 cohort comprised solely of participants of JD. Dosing in each MAD cohort did not occur until the SRC reviewed the data from a corresponding or higher dose level in the SAD study, and concluded it was safe and well-tolerated.

Overall, it was planned that 40 healthy participants participate, with 8 participants in each cohort. Within each cohort 6 participants were to be randomized to receive AZD5462 and 2 randomized to receive placebo for 10 days. On Day 1 and Day 10, participants received a single dose of AZD5462 or placebo, with BID dosing on Day 2 through Day 9. Timing for commencement of repeated dosing may have been adjusted based on emerging data. Participants remained at the clinic from Day -4 and up to 24 hours (approximately 5 times the predicted plasma half-life) after the last dose (Day 10), before discharge on Day 11.

Study Participants:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
Part A – 64 participants	56 participants	56 participants
Part B – 40 participants	42 participants	36 participants

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Main Inclusion Criteria:

- Healthy male and female (of non-childbearing potential) participants aged 18 to 50 years of age and healthy participants of JD, 20 to 50 years of age, with suitable veins for cannulation or repeated venipuncture.
- Have a body mass index (BMI) between 18 and 32 kg/m^2 inclusive and weigh at least 50 kg and no more than 105 kg, inclusive.
- For cohorts comprised solely of participants of JD, a participant was considered of JD only if both parents and all grandparents are Japanese.

Investigational products:

Formulations:	Strength/Concentrations:	Batch/Manufacturing Lot Numbers:	Expiry Dates:
AZD5462 – Oral solution	10 mg/mL	CCI CCI CCI	CCI CCI CCI
Placebo – Oral solution	Not applicable	CCI	CCI

Duration of Study:

The duration for participants randomized to Part A of the study was up to 41 days (6 weeks), and for Part B up to 49 days (7 weeks).

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit (EPCU). The administration of all medications was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of investigational product (IP) administration.

Criteria for Evaluation:

Safety Variables:

Safety endpoints included adverse events (AEs) and serious adverse events (SAEs), vital signs (supine systolic and diastolic BP, orthostatic BP, HR, temperature, and respiratory rate), safety laboratory assessments (coagulation, hematology, clinical chemistry, and urinalysis), 12-lead electrocardiogram (ECG; safety and digital ECG [dECG]); telemetry, and physical examination.

Pharmacokinetic Parameters:

Pharmacokinetic parameters, including, but not limited to, Cmax, AUClast, AUCinf, and CLR.

Exploratory/Pharmacodynamic Variables:

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Statistical Methods:

Determination of Sample Size:

The sample size for both the SAD and MAD parts of the study were empirically determined to provide adequate safety, tolerability, and PK data to achieve study objectives, while exposing as few participants as possible to the IP and study procedures.

Presentation and Analysis of Safety and Tolerability Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment cohort. The analysis of the safety variables was based on the safety analysis set.

Presentation and Analysis of Pharmacokinetic Data:

The plasma concentrations of AZD5462 and the PK parameters were listed and presented in tabular and graphical form as appropriate according to the most recent version of the AstraZeneca Corporate CSR or higher-level document (CSRHLD) tables, figures, and listings standards, that includes applicable descriptive statistics, as well as final table, figure, and listing shells that define handling of individual concentrations below the lower limit of quantitation (LLOQ) for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data. The analysis was based on the PK analysis set for both Part A and Part B.

Presentation and Analysis of Exploratory/Pharmacodynamic Data:

Exploratory or PD endpoints were summarized at each time point by treatment cohort. Each of the AZD5462 treatment cohorts and pooled placebo were compared at each time point using analysis of covariance (ANCOVA), adjusting for treatment and baseline measurement. Each endpoint was presented graphically for all post-baseline time points including the Follow-up Visit. Results for the CCI were listed and summarized by participant. The results of any exploratory analyses may not be reported in the CSR (see objectives/endpoints). The analysis was based on the safety analysis set for both Part A and Part B.

Protocol Deviations:

There was 1 (16.7%) participant with 1 important protocol deviation in Part B (AZD5462 500 mg twice daily [BID]); the participant did not finish dosing due to emesis.

No other important protocol deviations were reported. None of the important protocol deviations were judged to affect any of the pre-specified endpoints. Therefore, no participant with an important protocol deviation was excluded from the analysis.

Safety Results:

There were no deaths, SAEs, or any other significant AEs in the study. There were 3 participants in Part B who experienced AEs leading to discontinuation of the IP.

In Part A, 12 (28.6%) participants experienced any AE in the pooled AZD5462 treatment cohort, and 1 (7.1%) participant experienced any AE in the pooled placebo cohort. The most common AEs in Part A were headache, GI disorders (nausea and abdominal pain), and medical device site dermatitis. Most AEs were mild (12 out of 13) in intensity with 1 AE of moderate intensity. No AEs of severe intensity were reported in Part A.

In Part B, 14 (43.8%) participants experienced any AE in the pooled AZD5462 treatment cohort, and 2 (20.0%) participants experienced any AE in the pooled placebo cohort. The most common AEs in Part B were nervous system disorders (dizziness, headache, somnolence), nausea, vomiting, chills, and orthostatic

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HR response increased. Most AEs were mild (14 out of 16) in intensity with 1 AE of moderate in intensity, and 1 AE of severe intensity (dizziness).

No clinically relevant trends were observed for laboratory parameters. A trend in systolic and diastolic BP decrease and a trend in HR increase were observed. No AEs of hypotension were reported. No other clinically relevant trends were observed for vital signs, physical examinations, and ECGs.

The COVID-19 pandemic did not impact the overall safety results of this study (only 1 participant discontinued the IP due to a positive COVID-19 cases reported during the study).

No major safety and tolerability concerns were identified in this study in doses up to the highest dose given (CCI Part A [SAD] and CCI BID Part B [MAD]). CCI . Pre-specified study stopping criteria were not met.

Pharmacokinetic Results:

- AZD5462 was rapidly absorbed following single and multiple twice daily oral administration with a median tmax between 0.53 h and 1.75 h across all cohorts with no apparent trend with dose, day, or ethnicity.
- Half-life appeared to be longer at steady state, with no consistent trend in dose or ethnicity. Geometric mean t½λz ranged between 1.325 h and 6.32 h on Day 1 and between 2.216 h and 9.012 h on Day 10, with no consistent trend in dose or ethnicity. The apparent increase in t½λz observed at steady state is likely due to the less robust capture of the terminal phase.
- The geometric mean CL/F appeared to decrease with increasing dose with no trend observed with ethnicity.
- CCI
- Increase in steady state exposure with dose appeared to be supraproportional over the range of CCI to CCI with no trend in ethnicity.
- There was minimal accumulation following twice daily dosing at all dose levels.
- AZD5462 may display time-dependent PK following multiple twice daily dosing at the CCI and CCI dose levels.
- Steady state appears to be achieved by Day 4 as judged by the Ctrough concentrations.
- A similar peak (Cmax) and total exposure (AUC) was observed between Japanese and non-Japanese participants following a CCI single dose.
- A similar peak (Cmax) but higher total exposure (AUC) was observed in Japanese participants following a CCI single dose. However, the wide confidence interval (CI) of the Cmax ratio indicates high uncertainty in this estimate.
- A higher peak (Cmax) but similar total exposure (AUC) was observed in Japanese participants compared to non-Japanese participants following single and multiple twice daily administration at CCI .

Pharmacodynamic Results:

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- CCI
- CCI .
- CCI
- CCI

Discussion and Conclusion:

- No major safety and tolerability concerns were identified in this study in doses up to the highest dose given (CCI Part A [SAD] and CCI Part B [MAD]). CCI

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Pre-specified study stopping criteria were not met. A trend in systolic and diastolic BP decrease and a trend in HR increase were observed. Overall, the IP was generally well-tolerated and there were no major safety concerns.

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- Increase in steady state exposure with dose appeared to be supraproportional over the range of CCI to CCI with no trend in ethnicity.
- There was minimal accumulation following multiple twice daily dosing at all dose levels.
- AZD5462 may display time-dependent PK following multiple twice daily dosing at the CCI and CCI dose levels.
- A similar peak (Cmax) and total exposure (AUC) was observed between Japanese and non-Japanese participants following a CCI single dose.
- A similar peak (Cmax) but higher total exposure (AUC) was observed in Japanese participants following a CCI single dose. However, the wide CI of the Cmax ratio indicates high uncertainty in this estimate.
- A higher peak (Cmax) but similar total exposure (AUC) was observed in Japanese participants compared to non-Japanese participants following single and multiple twice daily administration at CCI .
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Version and Date of Report: Final, 14 June 2023

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