2 SYNOPSIS

Title of Study:	A Phase I, Randomized, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AZD4831 following Multiple-ascending Dose Administration in Japanese and Chinese Healthy Volunteers	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D6580C00008	
Investigational Medicinal Products:	Test Product: AZD4831 Reference Product: Placebo to match AZD4831	
Indication Studied:	Heart failure with preserved ejection fraction (HFpEF)	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD, PPD.	
Study Center:	Parexel Early Phase Clinical Unit – Los Angeles	
Study Duration:	First subject first visit: 16 Jan 2020	Last subject last visit: 11 Mar 2021

Study Objective(s):

Primary objective:

- To investigate the safety and tolerability of AZD4831 following oral administration of multiple-ascending doses at steady-state in healthy Japanese and Chinese subjects.

Secondary objective:

- To characterize the multiple-dose pharmacokinetics (PK) of AZD4831 (in plasma and urine) including PK assessments on Day 1 and Day 10, assessing the time required to reach steady-state conditions and the degree of accumulation at steady-state in healthy Japanese and Chinese subjects.

Exploratory objective(s):

- CCI
- CCI

CCI

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Study Design:

This was a Phase I, randomized, single-blind, placebo-controlled, multiple-ascending dose (MAD), sequential-group study in healthy Japanese (Part 1, Cohorts 1, 2, and 3) and Chinese (Part 2, Cohort 4) male subjects, conducted at a single study center with 32 subjects aged 18 to 50 years. A randomization ratio of 3:1 (AZD4831 versus placebo) was used. Each of the cohorts had 8 subjects (6 on AZD4831 + 2 on placebo).

For each cohort, the study comprised:

- Screening Period of a maximum of 28 days.
- A Treatment Period during which subjects were resident in the study center from the day before first dosing with the Investigational Medicinal Product (IMP) (Day -1) until at least 48 hours after last dosing on Day 10; discharged on Day 12.
- Three Follow-up Visits on Day 14, Day 16 (± 1 day), and Day 20 (± 1 day).
- A Final Follow-up Visit on Day 24 (± 2 days).

Subjects received AZD4831 or placebo for 10 sequential dosing days (per protocol) as follows:

Part 1: Japanese subjects.

- Cohort 1: CCI , Cohort 2: CCI , Cohort 3: CCI .

Part 2: Chinese subjects.

- Cohort 4: CCI .

Study Subjects:

Planned for Inclusion:	Randomized:	Completed Study:
Up to 40 subjects	32 subjects	30 subjects

Main Inclusion Criteria:

Healthy male Japanese and Chinese subjects aged 18 to 50 years (inclusive at Screening), having a BMI between 18 and 30 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 100 kg inclusive.

Note: A Japanese subject was 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.

Note: A Chinese subject was defined as having both parents and 4 grandparents who were ethnically Chinese. This included second and third generation Chinese whose parents or grandparents were living in a country other than China.

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Main Exclusion Criteria:

Subjects were excluded if they had any clinically significant illness or disease that would have influenced the results of the study, specifically previous or current thyroid disease, infections (particularly fungal infections), gastrointestinal hepatic or renal disease, skin disorders or significant allergies/hypersensitivity. Furthermore, subjects were excluded if they had any abnormal laboratory findings (including serology), vital signs or electrocardiogram (ECG) values at Screening and/or Day -1. Subjects were not allowed to have smoked within 3 months of Screening and for the duration of the study, used any medication within 2 weeks of first administration of IMP or have had a history of excessive alcohol intake or excessively consumed caffeine-containing drinks or food. The use of drugs of abuse was also prohibited. The use of drugs with enzyme inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP was excluded. Vulnerable subjects (e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order) and vegan subjects (subjects having dietary restrictions) were not considered for inclusion. Subjects were excluded if they donated plasma within 1 month of Screening or had any blood donation/blood loss of > 500 mL during the 3 months before Screening. Subjects were also excluded if they had received a new chemical entity (compound not approved for marketing) within 1 month of the first administration of IMP in this study (exclusion began 1 month after the final dose of the previous chemical entity or last visit in the previous study, whichever was the longest). Subjects who consented to participate in the optional genetic research were also excluded if they had had a previous bone marrow transplant or received a non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Investigational Medicinal Product: Adjust as per CSP

Formulation:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number:**	**Date of Manufacture:**
AZD4831	Oral suspension, CCI	CCI	CCI
Placebo to match AZD4831	Oral suspension, placebo	CCI	CCI

Duration of Treatment:

In all dosing cohorts, each subject received an oral dose of AZD4831 or placebo once daily for 10 consecutive days.

Each subject was involved in the study for approximately 8 to 9 weeks.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit. Compliance was assured by direct supervision and witnessing of study drug administration. After IMP administration, a check of the subject's mouth and hands was performed. Administration of IMP was recorded in ClinBase™.

All subjects randomized to receive the placebo and CCI AZD4831 (Cohort 1) (Japanese subjects) received all planned doses of IMP. Five of the 6 Japanese subjects received and completed the CCI AZD4831 cohort (Cohort 2). Three of the 6 Japanese subjects received and completed the CCI AZD4831 cohort (Cohort 3). Five of the 6 Chinese subjects received and completed the CCI AZD4831 cohort (Cohort 4).

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Criteria for Evaluation:

Pharmacokinetic Parameters:

Plasma:

- Cmax, Cmax/D, tmax, Ctrough, t½λz, AUCτ, AUCτ/D, CL/F, Vz/F, AUCinf, AUCinf/D, Rac(AUC), and Rac(Cmax)

Urine:

- Ae(t1-t2), Ae(0-last), %fe(t1-t2), %fe(0-last), and CLR

Pharmacodynamic Parameters:

Not Applicable.

Safety Variables:

- Adverse Events (AEs).
- Vital Signs (blood pressure, pulse, and tympanic temperature).
- Resting 12-lead Electrocardiogram (ECG).
- Digital(d)ECG.
- Telemetry.
- Physical Examination and Body Weight.
- Skin Rash
- Laboratory Assessments.

Viral serology and urine drugs of abuse, alcohol and cotinine were assessed for eligibility. The use of concomitant medication was also assessed and reported.

Exploratory Variables:

- CCI [redacted]
- CCI [redacted]

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Statistical Methods:

Determination of Sample Size:

The sample size 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 used was reasonable to accomplish the objectives of the study.

Part 1 Analysis – Cohorts 1 through 3:

After Cohorts 1 through 3 (Part 1 of the study with Japanese subjects) completed the last subject last visit, a soft database lock was performed for analysis of all safety and PK data for Part 1. The results of these safety and PK analyses of data from the Japanese subjects was used to determine the need for Cohort 5 and to inform subsequent studies in this population. Subsequently, Cohort 5 was not enrolled in this study.

Presentation and Analysis of Pharmacokinetic Data:

Pharmacokinetic blood sample collection times, including derived sampling time deviations, were listed. A listing was provided of the urine sample collection start and stop times, as well as volume. Plasma and urine concentrations and PK parameters were summarized by dose level, study day, and ethnicity using descriptive statistics. Individual plasma concentrations versus actual time, as well as combined individual plasma concentration per dose level versus actual times, were plotted in linear and semi-logarithmic scale, with separate plots for dose level and study day. The power model was used to analyze dose proportionality. In addition, figures of dose-normalized Cmax and AUCτ versus dose showing individual values and geometric mean were presented separately for each PK parameter.

Presentation and Analysis of Pharmacodynamic Data:

CCI [redacted]

Presentation and Analysis of Safety Data:

Subject disposition was listed and summarized, including the number of withdrawals and the primary reason for withdrawal. Subjects excluded from any analysis set were listed, including the reasons for exclusion. All safety data were presented in the data listings. Use of concomitant medication was reported. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). Additional summaries by severity and causality were presented. Vital signs measurements, digital ECGs (dECGs), and laboratory assessments (including hematology, serum clinical chemistry, thyroid panel, and immunology) were listed and summarized including changes from baseline. Additional listings were presented for urinalysis, the results of viral serology, and drugs of abuse, alcohol and cotinine screen. Any out-of-range laboratory results was flagged in the individual listings. Telemetry, physical examination, and 12-lead safety ECG data were listed only. Results of the ECGs, including normal/abnormal and specific findings, were listed.

Presentation and Analysis of Exploratory Data:

CCI [redacted]

Protocol Deviations:

There were no subjects with important protocol deviations.

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Pharmacokinetic Results:

- AZD4831 was rapidly absorbed with a median tmax between 0.51 and 2.00 hours across all 4 cohorts.
- Plasma concentrations declined after Cmax in an essentially biphasic manner.
- Geometric mean t½λz ranged between 50.15 and 57.75 hours with no consistent trend with dose or ethnicity.
- Increase in both Cmax and AUCτ with dose was slightly supra-proportional, although this result was not statistically significant.
- Accumulation was observed following multiple dosing. Geometric mean Ra(AUC) ranged between 2.337 and 2.737 across all 4 dose groups.
- Approximately 50% to 60% of the dose was excreted in urine. The fraction excreted in urine increased slightly with dose.
- Inter-subject variability was generally low (< 25%) to moderate (25% to 40%) but was moderate to high (> 40%) in the CCI Japanese group.
- The PK profile and parameters were generally similar between Japanese and Chinese subjects.

Pharmacodynamic Results:

Not applicable.

Safety Results:

- AZD4831 was generally well tolerated at CCI and CCI, with the exception of reported cases of rash (maculopapular rash CTCAE Grade 1 to 2 at CCI). The CTCAE Grade 2 maculopapular rash was also reported at CCI. Maculopapular rash is an identified risk for AZD4831. There were no new clinically significant safety findings for AZD4831 in this study.

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Discussion:

In this MAD study, healthy male Japanese (24) and Chinese (8) subjects were randomized into 4 cohorts of 8 subjects each to receive AZD4831 or placebo at daily (10 consecutive days) doses of CCI across 3 dosing cohorts with Japanese subjects and CCI in a single cohort with Chinese subjects. Originally, the plan was to also have a fifth optional dosing cohort, a Japanese dosing cohort where subjects were to receive CCI AZD4831 or placebo (6:2). This optional cohort was not enrolled.

Based on data from the Japanese cohorts (where 1 out of 6 subjects in Cohort 2 [CCI AZD4831] reported rash [maculopapular rash CTCAE Grade 1] and where 3 out of 6 subjects in Cohort 3 [CCI AZD4831] reported rash [maculopapular rash CTCAE Grades 2]), the provisional maximal dose of CCI for the Chinese cohort was set to CCI.

The sample size for the current study was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of subjects to this novel compound at this phase of clinical development.

The TEAEs experienced by 9 of the 24 (7 Japanese and 2 Chinese) subjects that received AZD4831 were mild to moderate in intensity. Rash was reported for PPD subject at CCI AZD4831 (maculopapular rash CTCAE Grade 1), PPD subjects at CCI AZD4831 (maculopapular rash CTCAE Grade 2), and PPD subject at CCI AZD4831 (maculopapular rash CTCAE Grade 2).

No deaths or SAEs were reported during the study.

The only out-of-range safety measurements that were considered clinically significant in the opinion of the Investigator, were the PPD of abnormal physical examination findings of generalized rash (CCI AZD4831) and PPD of pyrexia (CCI AZD4831).

The PK parameters were sufficiently and robustly characterized with no important protocol deviations which affected the PK.

AZD4831 was rapidly absorbed, reaching Cmax between 0.5 and 4 hours post-dose in all subjects. Elimination was biphasic, with a t½λz of over 2 days. Renal clearance of unchanged AZD4831 was an important route of elimination and accounted for between approximately 40% and 60% of total plasma clearance.

The PK was essentially similar in Japanese and Chinese subjects. Slightly higher exposures were observed in Chinese subjects; however, this observation may simply be a consequence of inter-subject variability.

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Conclusions:

Primary objective

- AZD4831 was generally well tolerated at CCI [redacted], with the exception of reported cases of rash (maculopapular rash CTCAE Grade 1 to 2 at CCI). The CTCAE Grade 2 maculopapular rash was also reported at CCI. Maculopapular rash is an identified risk for AZD4831.

Secondary objectives

- AZD4831 was rapidly absorbed with a median tmax between 0.51 and 2.00 hours across all 4 cohorts.
- Plasma concentrations declined after Cmax in an essentially biphasic manner.
- Geometric mean t½λz ranged between 50.15 and 57.75 hours with no consistent trend with dose or ethnicity.
- Increase in exposure with dose was slightly supra-proportional, although this result was not statistically significant.
- Accumulation was observed following multiple dosing. Geometric mean Ra(AUC) ranged between 2.337 and 2.737 across all 4 dose groups.
- Approximately 50% to 60% of the dose was excreted in urine. The fraction excreted in urine increased slightly with dose.
- Inter-subject variability was generally low (< 25%) to moderate (25% to 40%) but was moderate to high (> 40%) in the CCI Japanese group.
- The PK profiles and parameters were generally similar between Japanese and Chinese subjects.

Version and Date of Report: Final, dated 31 August 2021

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