- **Protocol number: D8330C00001**
- **Document title: A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)**
- **NCT number: NCT04630067**
- **Version number: 3.0**
- **Date of the document: Original Protocol - 09 Mar 2023**
  Protocol Amendment No. 1 - 28 Mar 2023

Clinical Study Report

1 TITLE PAGE

A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)

Investigational Medicinal Products:	AZD3427 (Relaxin-FC) and matching placebo
Indication Studied:	Heart failure
Parexel Study Number:	CCI [redacted]
Sponsor Study Number:	D8330C00001
IND Number:	151646
Development Phase:	Phase Ia/b
Sponsor:	AstraZeneca AB, 151 85 Södertälje, Sweden
Investigator Name and Address:	Part A: PPD Parexel Early Phase Clinical Unit (Baltimore) Harbor Hospital 3001 S. Hanover St. Baltimore, MD 21225 USA PPD Parexel Early Phase Clinical Unit (Los Angeles) 1560 E. Chevy Chase Drive, Suite 140 Suite 170 Glendale, CA 91206 USA Part B: Conducted at 8 centers in the USA
Study Duration:	17 Nov 2020 (first subject first visit) to 14 Sep 2022 (last subject last visit)
Version and Date of Report:	Final 3.0, dated 28 March 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Title of Study:	A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)	
Study Numbers:	Parexel Study No.: CCI [redacted] Sponsor Study No.: D8330C00001	
Investigational Medicinal Products:	AZD3427 (Relaxin-FC) and matching placebo	
Indication Studied:	Heart failure	
Development Phase:	Phase Ia/b	
Sponsor:	AstraZeneca AB, 151 85 Södertälje, Sweden	
Principal Investigator (PI):	PPD [redacted] PI at 8 centers in the USA	
Study Centers:	Part A: Parexel Early Phase Clinical Unit – Baltimore Parexel Early Phase Clinical Unit – LA Part B: 8 centers in the USA	
Publication:	None	
Study Duration:	First subject first visit: 17 Nov 2020	Last subject last visit: 14 Sep 2022

Study Objectives:

Primary objective:

- To assess the safety and tolerability of single and multiple ascending doses of AZD3427

Secondary objectives:

- To evaluate the pharmacokinetics (PK) of single and multiple ascending doses of AZD3427
- To evaluate the immunogenicity of single and multiple ascending doses of AZD3427

Exploratory objectives:

Part A and B:

- To explore the effect of AZD3427 on exploratory biomarkers

Part A only:

- To explore the effect of AZD3427 on hemodynamics
- To characterize the effect of AZD3427 on ventricular repolarization (QTcF interval)

Part B only:

- To characterize the effect of AZD3427 on markers of myocardial strain and necrosis
- To characterize the effect of AZD3427 on cardiac function
- To explore the effect of AZD3427 on arterial stiffness

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Study Design:

This was a Phase Ia/b, randomized, single-blinded, placebo-controlled, FTIH study to evaluate the safety, tolerability, PK, and immunogenicity of single and multiple ascending doses of AZD3427. The study was performed in 2 parts, Part A and Part B. Part A was a single ascending dose (SAD) study in healthy volunteers (males and females of non-childbearing potential). Part B was a multiple ascending dose (MAD) study in patients diagnosed with heart failure (HF) (males and females of non-childbearing potential).

Part A of the study comprised:

- A Screening Period: Maximum 27 days with one or more Screening Visits.
- A Treatment Period: Following confirmation of eligibility, healthy volunteers were admitted to the study center on Day -1. Randomization occurred either on Day -1 or Day 1 and IMP administration was performed on Day 1. Healthy volunteers were resident at the study center until 2 days after IMP administration (Day 3).
- A Follow-up Period: There were 8 Follow-up Visits (5 on-site visits, 3 telephone calls) with the last visit taking place at least 50 days after the IMP dose.

56 healthy volunteers in Part A were randomized to one of 7 cohorts with one cohort being exclusively of Japanese-descent. Healthy volunteers were randomized to receive a single dose of IMP (AZD3427 or placebo, in a 6:2 ratio). Healthy volunteers in cohorts 1a, 2a, 3a, 4a, and 7a received a single subcutaneous (SC) dose of AZD3427 in escalating dose levels of CCI respectively. Cohort 5a received a single intravenous (IV) dose of CCI AZD3427. Cohort 6a (Japanese-descent) received a single SC dose of CCI.

Sentinel dosing was performed in each cohort with at least 48 hours post-dose observation at the study center. The 48-hour post-dose safety data from the sentinel healthy volunteers was reviewed before dosing any additional healthy volunteers.

Part B of the study comprised:

- A Screening Period: Maximum 27 days with one or more Screening Visits. Following Screening and confirmation of eligibility, patients underwent baseline echocardiography and arterial stiffness assessments within 7 days prior to randomization (Day -7 to -1).
- A Treatment Period: Patients were admitted to the study center on Day -1. Randomization occurred either on Day -1 or Day 1 and after the first IMP administration was performed on Day 1. Patients were resident at the study center until 48 hours after the first IMP administration (Day 3). Patients returned for 4 additional Q1W doses on Days 8, 15, 22, and 29 and remained at the study center for 2 hours of post-dose observations at each of these time points.
- A Follow-up Period: There were 7 Follow-up Visits (4 on-site visits, 3 telephone calls) with the last visit taking place at least 50 days after the last IMP dose.

48 heart failure patients in Part B were randomized to one of 6 cohorts. Each cohort consisted of 8 participants, randomized in a 6:2 ratio to receive AZD3427 or placebo. Of these, 3 cohorts comprised of patients with heart failure with reduced ejection fraction (HFrEF) (Cohorts 1b, 3b, and 5b), and 3 cohorts comprised of patients with ejection fraction (EF) ≥ 41% (Cohorts 2b, 4b, and 6b). The doses were CCI (1b and 2b), CCI (3b and 4b), and CCI (5b and 6b). Across the cohorts, patients received a Q1W dose of AZD3427 or placebo for 5 weeks (ie, a total of 5 doses).

<table>
<tr><td>Title of Study:</td><td colspan="2">A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)</td></tr>
<tr><td colspan="3">Study Subjects:</td></tr>
<tr><td>Planned for Inclusion:</td><td>Randomized:</td><td>Completed Study:</td></tr>
<tr><td>56 healthy volunteers (Part A)
48 heart failure patients (Part B)</td><td>48 healthy volunteers (Part A, Set 1)
8 healthy volunteers (Part A, Set 2)
8 healthy volunteers (Part A, Set 3)
24 heart failure patients (Part B, HFrEF)
24 heart failure patients (Part B, HF with EF ≥ 41%)</td><td>48 healthy volunteers (Part A, Set 1)
8 healthy volunteers (Part A, Set 2)
8 healthy volunteers (Part A, Set 3)
23 heart failure patients (Part B, HFrEF)
24 heart failure patients (Part B, HF with EF ≥ 41%)</td></tr>
<tr><td colspan="3">Main Inclusion Criteria:
Both Part A & B:
• Provision of signed and dated, written informed consent prior to any study-specific procedures.
• Females must have had a negative pregnancy test at the Screening Visit, must not have been lactating and must have been of non-childbearing potential.
Part A:
• Females must have had a negative pregnancy test on admission to the study center.
• Male healthy volunteers and female healthy volunteers (of non-childbearing potential) aged 18 to 50 (inclusive) years, with suitable veins for cannulation or repeated venipuncture.
• Healthy volunteers with no underlying disease, at the discretion of the Investigator.
• Had a BMI between 18 and 30 kg/m^2 inclusive and weigh at least 55 kg and no more than 100 kg (inclusive).
• For Cohort 6a, healthy volunteers must have been of Japanese-descent. A healthy volunteer was considered Japanese if both parents and all grandparents are Japanese.
Part B:
• Male patients and female patients (of non-childbearing potential) aged 18 to 75 (inclusive) years, with suitable veins for cannulation or repeated venipuncture.
• Had a known clinical diagnosis of Stage C HF (NYHA Class I to III) and been on stable medical therapy for at least 12 weeks prior to Screening with no significant dose change or new medications added during that period.
• Cohorts 1b, 3b, 5b: Patients with a diagnosis of HFrEF defined as EF ≤ 40%.
• Cohorts 2b, 4b, 6b: Patients with a diagnosis of HF with EF ≥ 41%.
• Had a BMI between 18 and 40 kg/m^2 (inclusive) and weigh at least 55 kg and no more than 136 kg (inclusive).</td></tr>
</table>

Title of Study:	A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)
Investigational Medicinal Product(s):	
AZD3427 for Subcutaneous Administration	
Supplier:	AstraZeneca
Formulation:	CCI [redacted]
Strength/concentration:	CCI [redacted]
Dose:	A dose range was studied. **Part A:** • Cohort 1a: CCI [redacted] • Cohort 2a: CCI [redacted] • Cohort 3a: CCI [redacted] • Cohort 4a: CCI [redacted] • Cohort 6a: CCI [redacted] • Cohort 7a: CCI [redacted] **Part B:** • Cohorts 1b, 2b: CCI [redacted] • Cohorts 3b, 4b: CCI [redacted] • Cohorts 5b, 6b: CCI [redacted]
Route of administration:	SC
Specific device for drug administration, if applicable:	1 mL, 2 mL, or 3 mL (depending upon site preference) polypropylene syringes for SC injection. Syringes and needles for injection were provided by the Parexel study centers/non-Parexel sites.
Regimen:	SAD (Part A) and MAD (Part B)
Batch/Manufacturing Lot Number(s):	CCI [redacted]
Expiry Date(s):	31 May 2023
Placebo for Subcutaneous Administration	
Supplier:	AstraZeneca
Formulation:	CCI [redacted]
Strength/concentration:	NA
Dose:	NA
Route of administration:	SC

Title of Study:	A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)
Specific device for drug administration, if applicable:	1 mL, 2 mL, or 3 mL (depending upon site preference) polypropylene syringes for SC injection. Syringes and needles for injection were provided by the Parexel study centers/non-Parexel sites
Regimen:	SAD (Part A) and MAD (Part B)
Batch/Manufacturing Lot Number(s):	CCI [redacted]
Expiry Date(s):	31 October 2023
AZD3427 for Intravenous Administration	
Supplier:	AstraZeneca
Formulation:	CCI [redacted]
Strength/concentration:	CCI [redacted]
Dose:	**Part A:** • Cohort 5a: CCI [redacted]
Route of administration:	IV
Specific device for drug administration, if applicable:	20 mL polypropylene syringes for IV injection/infusion with a syringe pump.
Regimen:	Single dose
Batch/Manufacturing Lot Number(s):	CCI [redacted]
Expiry Date(s):	31 May 2023
Placebo for Intravenous Administration	
Supplier:	AstraZeneca
Formulation:	CCI [redacted]
Strength/concentration:	NA
Dose:	NA
Route of administration:	IV
Specific device for drug administration, if applicable:	20 mL polypropylene syringes for IV injection/infusion with a syringe pump.
Regimen:	Single dose

Title of Study:	A Phase Ia/b Randomized, Single-blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of Single Ascending Doses of AZD3427 in Healthy Volunteers and Multiple Ascending Doses of AZD3427 in Patients with Heart Failure (HFrEF and HF with EF ≥ 41%)
Batch/Manufacturing Lot Number(s):	CCI [redacted]
Expiry Date(s):	31 October 2023

Study Duration:

Part A: Each healthy volunteer was involved in the study for approximately 11 weeks

Part B: Each patient was involved in the study for approximately 15 weeks

Treatment Compliance:

Dosing took place at the study center(s). The administration of all medications was recorded in the EDC system. Compliance was assured by direct supervision and witnessing of IMP administration. Bioanalysis of the Day 8-serum sample from all presumed placebo-treated subjects were used to confirm lack of AZD3427 in the serum.

Criteria for Evaluation:

Safety Variables:

Safety endpoints included adverse events (AEs), clinical laboratory analysis (hematology, clinical chemistry, urinalysis, and coagulation), vital signs (blood pressure, heart rate, respiratory rate, body temperature), 12-lead electrocardiograms (ECGs), telemetry, physical examination, and injection site reactions.

Pharmacokinetic Parameters:

Non-compartmental PK parameters, including, but not limited to: Observed maximum serum concentration (Cmax), area under serum concentration-time curve from time zero to time of last quantifiable AZD3427 concentration (AUClast), area under serum concentration-time curve from time zero extrapolated to infinity (AUCinf), area under serum concentration-time curve from time zero to 168 hours post-dose administration (AUC0-168), time to reach maximum serum concentration (tmax), and terminal half-life (t½λz).

Immunogenicity parameters:

Anti-drug antibodies (ADAs), neutralizing antibodies (NAbs), and ADA titers.

Exploratory Variables (to be reported in the CSR):

Pharmacodynamic (PD) Parameters:

Part A: Cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), cardiac index (CIx), stroke volume index (SVI), total peripheral resistance index (TPRI).

Part B: N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Troponin T, left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LV GLS), pulse wave analysis (PWA), pulse wave velocity (PWV).

Biomarker Parameters:

Pharmacodynamic biomarkers (Part A and B), urine albumin creatine ratio (ACR) (Part B only), other exploratory biomarkers (Part A and B).

Statistical Methods:

All results were calculated and presented separately for each study part.

In Part A, the analysis was performed in 3 sets:

- Set 1: For Cohorts 1a to 4a, 6a, and 7a, the analysis was presented by treatment group (pooled placebo from all cohorts and AZD3427 SC CCI , CCI for the Japanese-descent, and CCI)
- Set 2: For Cohort 6a (Japanese-descent), analysis was presented by treatment group (placebo and AZD3427 SC CCI)
- Set 3: For Cohort 5a (IV cohort), the analysis was presented by treatment (placebo and AZD3427 IV CCI)

In Part B, all analyses were performed separately for HFrEF and HF with EF ≥ 41% cohorts. The placebo data from the HFrEF cohorts (Cohort 1b, 3b, and 5b) was pooled together and the placebo data from the HF with EF ≥ 41% cohorts (Cohort 2b, 4b, and 6b) was pooled together, with at least 6 patients in each pooled placebo group.

Presentation and Analysis of Safety Data:

Safety analysis was based on the as-treated population. All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (number [n], mean, standard deviation [SD], minimum [min], median, maximum [max]) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment. Adverse events were summarized by preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and adverse events leading to the discontinuation of IMP (DAEs) were made and the number of subjects who had any AEs, SAEs, DAEs, and AEs with severe intensity were summarized. Adverse events that occurred before dosing were reported separately. Tabulations and listings of data for vital signs, clinical laboratory tests, digital electrocardiograms, 12-lead ECGs (listing only), telemetry (listing only), and injection site reactions (listing only) were presented.

Presentation and Analysis of Pharmacokinetic Data:

For PK endpoints, non-compartmental analysis was performed for AZD3427-treated subjects based on the PK population. The serum AZD3427 concentrations and the PK parameters were listed and presented in tabular and graphical form as defined in the statistical methods section of the clinical study protocol (CSP). All PK parameters were summarized for AZD3427 by dose level and cohort using appropriate descriptive statistics, based on the PK population. Individual concentration-time data was graphically presented on linear and semi-logarithmic scales for the as-treated population. Combined individual serum concentration versus actual times were plotted on both the linear and semi-logarithmic scale for all subjects in the PK population.

Inferential statistical analyses were performed for both parts, as described in the CSP.

Presentation and Analysis of Immunogenicity Data:

Immunogenicity analysis was based on the immunogenicity population. The presence or absence of ADAs to AZD3427 reported, including the titer for samples confirmed positive for ADA for each dose level of AZD3427, was listed by subject and time point. The results of the ADA assessments were listed for each subject and time point. In addition, the ADA titers (n, median, min, and max) were summarized by treatment group and presented as defined above for all subjects with a positive confirmatory assay at each time point.

Presentation and Analysis of Pharmacodynamic (Exploratory) Data:

The PD analysis was based on the as-treated population (Part A) and ITT population (Part B). The results of the PD measurements were listed by subject and time point, including the date/time of the assessment, absolute and percentage changes from baseline, and repeat/unscheduled measurements. Descriptive statistics were presented by treatment (as defined above) and time points for both observed values and changes from baseline. Results were based on the as-treated population (Part A) and ITT Population (Part B). For each exploratory PD variable, each of the AZD3427 treatment groups and placebo (as defined above) were

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compared at each time point using analysis of covariance adjusting for treatment and baseline measurement. Changes from baseline were presented graphically for all post-baseline time points including the Follow-up Visit.

Determination of Sample Size:

The sample size was chosen to obtain reasonable evidence of safety, tolerability, and PKPD data 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 proposed was reasonable to accomplish the objectives of the study.

Protocol Deviations:

The number of participants with at least one important protocol deviation were as follows:

Part A (Set 1): 2 (5.6%) in the total AZD3427 group.

Part A (Set 2): none reported.

Part A (Set 3): 1 (16.7%) in the CCI AZD3427 IV group and 1 (50%) in the placebo group.

Part B (HFrEF): 6 (33.3%) in the total AZD3427 group and 1 (16.7%) in the pooled placebo group.

Part B (HF with EF ≥ 41%): 4 (22.2%) in the total AZD3427 group and 1 (16.7%) in the pooled placebo group.

None of the important protocol deviations was assumed to affect any of the pre-specified endpoints. No participants with an important protocol deviation were excluded from the analysis.

Pharmacokinetic Results:

- AZD3427 was slowly absorbed following single SC administration across the C to CCI AZD3427 dose range (median tmax range of 72 to 96 hours) with an absolute bioavailability of approximately 66%.
- AZD3427 administered SC declined in a multiphasic manner following Cmax. In Part A (single dose, healthy volunteers) the geometric mean terminal t½λz ranged from 162 to 214 hours (approximately 7 to 9 days) across the C to CCI dose range. In Part B (multiple doses, HF patients), the geometric mean terminal t½λz ranged from 315 to 325 hours (approximately 13 to 14 days) after the last dose at the dose levels of CCI and CCI .
- AZD3427 exposure after SC administration increased approximately proportionally with dose across the dose range in Part A (CCI to CCI) and in Part B (CCI to CCI).
- Following single IV dose of CCI AZD3427, AZD3427 declined in a multiphasic manner following Cmax with the geometric mean terminal t½λz of 117 hours (approximately 5 days).
- The overall exposure (AUC) to AZD3427 was similar at the same SC single dose (CCI) between the Japanese-descent healthy volunteer cohort and the healthy volunteer cohort. However, Cmax was approximately CCI lower in the Japanese-descent healthy volunteer cohort compared to the healthy volunteer cohort.
- The exposure to AZD3427 administered SC was similar between patients with HFrEF and patients with HF with EF ≥ 41%.

Safety Results:

Part A

Single ascending SC doses of AZD3427 (CCI) and an IV CCI dose administered to healthy volunteers, including volunteers of Japanese-descent, were well tolerated and there were no safety concerns.

These conclusions are based on the following results:

- There were no SAEs, deaths, or AEs leading to discontinuation of IMP or withdrawal from the study.
- Overall, 9 (25.0%) healthy volunteers in the total AZD3427 group and 2 (16.7%) healthy volunteers in the pooled placebo group in Set 1 experienced at least one AE.
- There were no AEs reported in Set 2.
- Overall, 3 (50.0%) healthy volunteers in the IV CCI AZD3427 group and none in the pooled placebo group in Set 3 experienced at least one AE.
- There were no notable trends for AEs by SOC or PT. By PT, back pain was the only AE reported more than once (reported by 2 healthy volunteers).
- Overall, 5 (13.9%) healthy volunteers in the total AZD3427 group and 2 (16.7%) healthy volunteers in the pooled placebo group in Set 1 had at least one AE considered possibly related to IMP as assessed by the Investigator.
- Overall, 2 (33.3%) healthy volunteers in the IV CCI AZD3427 group in Set 3 had at least one AE considered possibly related to IMP as assessed by the Investigator. By PT no AEs were reported more than once.
- The majority of AEs were of mild intensity and there were no AEs of severe intensity.
- Two healthy volunteers had injection site reactions, one in the CCI group and one in the CCI group. Both reactions were mild in intensity.
- No severe hypersensitivity reactions were reported.
- No clinically relevant trends were observed for laboratory results, vital signs, physical examinations, and ECGs and no safety concerns were raised.

Part B

Multiple doses of AZD3427 (CCI) administered to patients with heart failure were well tolerated with no major safety concerns.

These conclusions are based on the following results:

- There were no deaths.
- There were 2 SAEs reported in the HFrEF Set.
  - One patient in the CCI AZD3427 group reported an SAE of back pain of moderate intensity, which was not considered to be possibly related to the IMP by the Investigator.
  - One patient in the CCI AZD3427 group reported an SAE of COVID-19 of moderate intensity, which was not considered to be possibly related to the IMP by the Investigator.
- One patient reported an AE that led to discontinuation of the IMP (SARS-CoV-2 test positive in the CCI group HFrEF set).
- Overall, 11 (61.1%) patients in the total AZD3427 group and 2 (33.3%) patients in the pooled placebo group in the HFrEF set experienced at least one AE.
- Overall, 14 (77.8%) patients in total AZD3427 group and 4 (66.7%) of patients in the pooled placebo group in the HF with EF ≥ 41% set experienced at least one AE.
- There were no notable trends for AEs by SOC or PT in the HFrEF set.
- Eight AEs of hypotension were reported in 6 patients.
  - Hypotension was the most frequently reported AE in the HF with EF ≥ 41% set, reported in 5 patients, 3 patients in the CCI AZD3427 group and 2 patients in the CCI AZD3427 group. All were mild in intensity and assessed by the Investigator as possibly related to IMP (no patients were discontinued from the study or the IMP).

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- ° One AE of hypotension was reported in the HFrEF set CCI AZD3427 group, which was mild in intensity and was not considered possibly related to the IMP by the Investigator.
- The majority of AEs were of mild or moderate intensity PPD
- In Part B patients there was a mild transient reduction of hemoglobin and hematocrit levels relative to placebo. No other clinically relevant findings were observed for any of the other laboratory parameters.
- Two patients had injection site reactions, one in the CCI HF with EF ≥ 41% group and one in the CCI HFrEF group. Both reactions were mild in intensity.
- No severe hypersensitivity reactions were reported.
- No clinically relevant trends were observed for vital signs, physical examinations, and ECGs and no safety concerns were raised.
- Three COVID-19/SARS-CoV-2 test positive AEs were reported in the HFrEF set. However, the COVID-19 pandemic was not judged to impact the safety results of this study.

Immunogenicity Results:

There were no participants with treatment-emergent ADAs. One healthy volunteer in the study (Part A, Set 3, IV CCI AZD3427 group) had pre-existing ADAs. The ADA titers reduced from CC at baseline to CC after administration of AZD3427.

Pharmacodynamic Results:

- For Part A, dose-dependent CCI increases were seen following treatment with AZD3427. These increases in the AZD3427 treatment groups were statistically significant versus pooled placebo at time points up to Day 29 for all treatment groups, except for the CCI AZD3427 SC group at Day 29. The C and CCI AZD3427 SC groups showed statistically significant increases at Day 50.
- For Part B, CCI increases were seen following treatment with AZD3427. Statistically significant differences in the AZD3427 treatment groups versus pooled placebo were seen from Day 2 through Day 57 for the CCI group, and from Day 2 through Day 78 for the CCI group. For the CCI AZD3427 group statistically significant differences were seen from Day 8 through Day 57. The CCI AZD3427 groups overall showed larger increase than the CCI AZD3427 group.
- Whilst some statistically significant differences were observed for AZD3427 versus placebo for the other PD parameters, there were no notable clinically relevant results.

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Discussion and Conclusion:

Pharmacokinetics

- AZD3427 was slowly absorbed following single SC administration across the CCI dose range (median tmax range of 72 to 96 hours) with an absolute bioavailability of approximately 66%.
- AZD3427 administered SC declined in a multiphasic manner following Cmax. In Part A (single dose, healthy volunteers), the geometric mean terminal t½λz ranged from 162 to 214 hours (approximately 7 to 9 days) across the CCI dose range. In Part B (multiple doses, HF patients), the geometric mean terminal t½λz ranged from 315 to 325 hours (approximately 13 to 14 days) after the last dose at the dose levels CCI and CCI .
- AZD3427 exposure after SC administration increased approximately proportionally with dose across the dose range in Part A (CCI to CCI) and in Part B (CCI to CCI).
- Following single IV dose of CCI AZD3427, AZD3427 declined in a multiphasic manner following Cmax with the geometric mean terminal t½λz of 117 hours (approximately 5 days).
- The overall exposure (AUC) to AZD3427 was similar at the same SC single dose (CCI) between the Japanese-descent healthy volunteer cohort and the healthy volunteer cohort. However, Cmax was approximately CCI lower in the Japanese-descent healthy volunteer compared to the healthy volunteer cohort.
- The exposure to AZD3427 administered SC was similar between patients with HFrEF and patients with HF with EF ≥ 41%.

Safety

- AZD3427 at all doses administered was well tolerated in both healthy volunteers and patients with heart failure and there were no major safety concerns.

COVID-19 Pandemic

- The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final 3.0, dated 28 March 2023

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