STATISTICAL ANALYSIS PLAN	
Study Code	D6580C00010
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A Randomised, Double-blind, Placebo-controlled, Multi-center Sequential Phase 2b and Phase 3 Study to Evaluate the Efficacy and Safety of AZD4831 Administered for up to 48 Weeks in Participants with Heart Failure With Left Ventricular Ejection Fraction > 40%

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CCI

[redacted]

LIST OF ABBREVIATIONS

List abbreviations and definitions of specialised or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialised Term	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
AEoSI	Adverse event of special interest
ALT	Alanine-Aminotransferase
ANCOVA	Analysis of covariance
AR [1]	Autoregressive order 1
ARH [1]	Heterogeneous autoregressive order 1
AST	Aspartate-Aminotransaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
CSR	Clinical Study Report
CCI	[redacted]
CSP	Clinical study Protocol
CV	Coefficient of Variation
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Adverse events leading to discontinuation of study medication
DRC	Development Review Committee
CCI	[redacted]
ECG	Electrocardiogram
eCDF	Empirical cumulative distribution function
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
FAS	Full analysis set
HbA1c	Haemoglobin A1c
HF	Heart Failure

HR	Hazard Ratio
hsCRP	High-sensitivity C-reactive protein
CCI	[redacted]
ICF	Informed consent form
IL-6	Interleukin 6
IP	Investigational Product
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
KCCQ	Kansas city cardiomyopathy questionnaire
KCCQ-TSS	Kansas city cardiomyopathy questionnaire – Total Symptom Score
KCCQ-OSS	Kansas city cardiomyopathy questionnaire – Overall Summary Score
KM	Kaplan-Meier
LAVI	Left atrial volume index
LLN	Lower Limit Normal
LLoQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
LV-GLS	Left ventricular global longitudinal strain
LVMI	Left ventricular mass index
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MMRM	Mixed model repeated measures
MPO	Myeloperoxidase
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York heart association
PDF	Probability distribution function
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient-reported outcome
PT	Preferred term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set

SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
T2DM	Type-2 Diabetes Mellitus
T4	Thyroxine
TA	Therapeutic Area
TB	Total bilirubin
TIBC	Total iron binding capacity
TSH	Thyroid stimulating hormone
UACR	Urinary albumin-to-creatinine ratio
ULN	Upper Limit Normal
ULoQ	Upper limit of quantification
URC	Unblinded review committee
UN	Unstructured
WHODD	WHO Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Version 1				
N/A	6/23/2021	Initial approved SAP	N/A	N/A
Version 2				
General	10/19/2022	Removal of all text describing statistical analysis for Part B of study. Removal of text in Introduction section describing Study design, Randomisation and Number of subjects. British English used throughout.	N/A	Agreement to have separate SAP for Part B of study. Avoid duplicate information. The SAP should not be read in isolation but in conjunction with the CSP. Consistency.
Timing of analysis	10/19/2022	Rewording.	Yes	To align with updated version of CSP (v5).
Multiple testing procedure	10/19/2022	Moving of section, now described in Section 3.3.4. Details given how alpha distributed and addition of testing order. Definition of primary comparison (AZD4831 Total vs placebo).	Yes	Align with SAP template. Clarification.

General study level definitions	10/19/2022	Rewording and addition of definitions for Study periods, Time at risk and censoring, and Unit conventions. **Baseline:** Addition to consider timepoint of assessment when data allows. **Handling of incomplete cases:** Removal of end-of-study definition. Censoring described in new Time at risk and censoring section (3.3.1.8). **Study day:** Renaming from Randomisation start date and study day to Study day.	Yes	Clarification. Align with CSP.
Visit window	10/19/2022	Removal of baseline and CCI [redacted] from Table 1. Analysis visit windows for these categories are described in Sections 3.3.1.1, 4.2.9.4 and 4.2.18.1.	Yes	Clarification.
Handling of scheduled and unscheduled visits	10/19/2022	Rewording. Change to allow unscheduled visit to replace scheduled visit if closer to target day.	Yes	To align with updated version of CSP (v5).
Handling of protocol deviations in study analysis	10/19/2022	Removal of referral to Appendix O	Yes	Appendix O is removed.

Study population	10/19/2022	Change of which categories are defined here and addition of the corresponding definitions. Rewording of presentation parts. Update of definition of Full analysis set.	Yes	Align with Study population TFL standards and with which data are collected in study. Clarification. Align with definition of FAS to be used in Part B of the study.
Endpoint analyses	10/19/2022	Changes in Table 2. Added details on Intercurrent event strategies and Population level summaries. Division of sections for each variable (or group of variables) to be analysed. Rewording. Addition of model specifications.	Yes	Align with analyses being performed. Align with Study objective and SAP template instructions. Clarification. Clarification.

Statistical analysis for primary endpoints	10/19/2022	Sensitivity analysis of primary endpoints changed to a supplementary analysis. New sensitivity analysis defined. New additional supplementary analyses defined. Estimands for new supplementary analyses defined. Clarification of estimands, specification of intercurrent events and handling of these, distinction made between intercurrent events and missing data. Addition of several biomarkers to subgroup analyses.	Yes	Planned sensitivity analysis was addressing a different estimand than the primary analysis, hence changed into a supplementary analysis. Align to estimand framework and SAP template. Align to estimand framework and SAP template. Further exploratory analysis to be made.
Statistical analysis for secondary endpoints	10/19/2022	CCI [redacted] Rewording of log-transformed variables and the corresponding analyses. CCI [redacted]	Yes	Align with updated version of CSP (v5). Clarification. CCI [redacted]

Statistical analysis for exploratory endpoints	10/19/2022	CCI [redacted]	Yes	CCI [redacted]

Safety analyses	10/19/2022	**Exposure:** For presentation: Total year of exposure added, Exposure over time curve added, cumulative categories added. **General safety** Removal of AE objective text in Section 4.6.2, instead Table 4 added. Definition of Safety estimand added. Definition of analyses for On-treatment and On-study periods added (see new Study periods Section 3.3.1.5). **Adverse events** Rewording of categories. Rewording and restructuring of AEoSI categories. Change of analysis and presentation of AEs from event rates to time-to-event analysis (KM%, KM% difference and HR) **Clinical laboratory, Blood sample:** Removal of referral to Urinalysis in this section. Rewording and restructuring. **Clinical laboratory, Urinalysis:** Rewording and restructuring. **Vital signs:**	Yes	Clarification. Clarification. Complementary analysis approaches added. Clarification. Align with TFL standards. Change of estimators. Clarification. Align with TFL standards. Clarification. Align with TFL standards. Clarification. Align with TFL standards.

		Rewording and restructuring. **ECG:** Change of outputs and presentation Addition of Orthostatic blood pressure test to **Other Safety Assessments** section.		Align with data collected. Align with CSP.
Interim analysis	10/19/2022	Rewording of timing of interim analysis. Reference to URC Charter added.	Yes	Align with updated version of CSP (v5).
References	10/19/2022	Removal of bibliography items.	Yes	Items are not used due to removal of Part B analyses and appendices.
Appendices	10/19/2022	Removal of appendices. Essential information moved to main sections where suitable.	Yes	Clarification and simplification of SAP. Only essential information kept in SAP.
Version 3				
Changes to protocol planned analyses	03/23/2023	Clarification of assumed standard deviation for KCCQ-TSS in sample size calculations.	No	Correction.
General study level definitions	03/23/2023	Addition of considering randomisation when imputing missing day value of adverse event dates. Removal of consideration taken to timepoint of first IP dose when deriving study periods.	Yes	Align with how other cases of incomplete adverse event dates are imputed. Simplification
Study periods	03/23/2023	Rewording of definitions of study periods ad censoring for time-to-event analyses, efficacy and safety.	Yes	Clarification

Covid-19	03/23/2023	Rewording of data collection of Covid-19 impact on study. Removal of referral to listing of subjects with reported issues in the CTMS due to Covid-19.	Yes	Align with data collection
Study population	03/23/2023	Definition of subjects completed treatment expanded to include subjects who died during follow-up. Argentina removed as country. Removal of tabulation of rescue medication related to rash	Yes	To allow number of subjects started treatment to equal number of subjects who discontinued or completed treatment. Align with countries included in study. Align with latest version of CSP.
Statistical analysis for primary endpoints	03/23/2023	'Unit' removed after S-Cystatin C	Yes	Correction of typo, unit not presented for subgroups defined by median.

Statistical analysis for secondary endpoints	03/23/2023	Population-level summary for primary and third supplementary estimand updated to include adjusted geometric mean for the log-transformed variables. Population-level summary in estimand table for subgroup analysis of log-transformed variables updated. Rule added for which IL-6 lab code to use in analysis if a subject have two reported lab codes on same visit. Two supplementary analyses added for IL-6 Addition that PK analysis is performed on FAS	Yes	Clarification Correction of typos. To handle addition of hs-IL-6 lab codes in analysis. To evaluate impact of two different laboratory analysis methods used. Clarification
Statistical analysis for exploratory endpoints	03/23/2023	CCI [redacted] [redacted]	Yes	Clarification Clarification
Exposure	03/23/2023	Addition to presentation of KM % plots of IP discontinuing event.	Yes	Improved overview and interpretation of data.

Safety analyses	03/23/2023	**Adverse events** Addition of KM % plots of AEoSIs. Maximum intensity and CTCAE grade categories changed to be cumulative. **Clinical laboratory, blood sample** Treatment emergent abnormality criteria comprising combinations of parameters are flagged when met on same visit, **ANCA** Mapping of negative and positive results added. **Vital signs** > changed to ≥ and 60 changed to 50 for Pulse rate shift from baseline categorisations.		Improved overview and interpretation of data. Improved overview and interpretation of data. Clarification Clarification Correction of typos.
Version 4				

General study definitions	03/08/2024	Remove mentioning of time when defining baseline. Only date will be considered. Updated definition of baseline for KCCQ to use first assessment if two assessments qualify as baseline on the same day. Replace 'time' by 'date' for deriving study periods. Removal of sentence when timepoint is missing. Update to use randomisation for derivation of the Planned treatment period. Typo in subsection title.		Clarification Clarification regarding the handing of an of an additional scenario Clarification to avoid misinterpreting time as timepoint when deriving study periods and correction of typo (unintentional leftover from the last SAP update when timepoints were removed). Correction Correction
Visit window	03/08/2024	Post-dose vital signs (in VS7 form) collected at day of randomization are included in visit 4 analysis window.		Clarification

Study population	03/08/2024	IP deviations added as IPD category to match Protocol Deviation Plan categories. Time from diagnosis of HF enrolment' category removed from baseline disease characteristics categories. Unit for neutrophil updated Neutrophil count category added to baseline disease characteristics categories.		Correction to match Protocol Deviation Plan categories. Correction Correction Correction
Timeframe for start of medication to be considered a concomitant medication is extended to match on-treatment period.	03/08/2024	Timeframe for start of medication to be considered a concomitant medication is extended. Rescue medications removed from presentation as part of concomitant medications.		Correction to match definition of on-treatment period. Correction, there is no rescue medication definition in the study.
Endpoint analyses	03/08/2024	Rescue medications removed as a potential intercurrent event in the estimand description since we do not have a rescue medication definition in the study. Updated wording in regarding concomitant medication in definition of estimands for primary and supplementary estimands.		Correction, there is no rescue medication definition in the study. Alignment with Safety estimand wording.

Statistical analysis for primary endpoints	03/08/2024	Updated threshold for HbA1C subgroup categories. Subgroup analysis: Denominator for 5 % (when separate models will be fitted for each subgroup category) changed from randomised subjects to FAS.		Correction of typo Correction
Statistical analysis for secondary endpoints	03/08/2024	IL-6 observations reported as LLoQ will be imputed as described in Section 3.3.1.3. Description of IL-6 categories for first supplementary analysis (logistic regression) updated. Update of second supplementary analysis (ANCOVA) to include all subjects with a matched pair of lab analysis method for IL-6. Method added as covariate in the model.		Clarification Correction of typo Correction

Statistical analysis for exploratory endpoints	03/08/2024	CCI [redacted] [redacted] [redacted] [redacted] **Time-to-CV event** Rescue medications removed as a potential intercurrent event in the estimand description for time-to-event analysis. Wording of 'adjudicated' updated to 'reported' for CV events. Time-to-event analysis is stratified by neutrophil count. CCI [redacted] CCI [redacted]		Clarification and alignment of windows for both analyses (descriptive and within-subject analysis). CCI [redacted] CCI Correction, there is no rescue medication definition in the study. Correction of typo, there is no adjudication in the study. Clarification CCI

		CCI [redacted]		CCI [redacted]
Safety analysis	03/08/2024	Data from the post-dose vital signs eCRF form VS7 will not be considered as baseline. The order for selecting data from eCRF forms for baseline vital signs will also be applied for post-randomisation visit. Overdose listing added.		Clarification Clarification Correction

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D6580C00010 Part A supporting the clinical study report. The reader is referred to the CSP and the CRF for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

A standard deviation of 20 points was assumed for KCCQ-TSS for the sample size calculations. No other changes to planned analyses.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

At least two, but possibly several, interim analyses will be performed by an internal study-independent Unblinded Review Committee (URC), with the purpose of informing further development of the clinical programme, including but not limited to dose selection to start Part B. The first interim analysis will be performed when at least 150 randomised subjects have had the possibility to reach the 16 weeks visit. One of the interim analyses will be performed when all subjects in Part A have completed the last protocol-specified visit/assessment. If Part B were not to start or progress, then the last interim analysis of Part A would be regarded as the final analysis and this will be used to write the CSR.

In addition, a Data Review Committee (DRC) will perform periodic analyses with focus on skin reactions and rashes, and general safety. These analyses are not in scope for this document and are described in a separate DRC charter.

3.2 Analysis Populations

See Sections 4.2, 4.6 and 4.2.16.1 for definitions of estimand populations.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Baseline

For the Full analysis set (FAS, see Section 4.1.2.1), baseline is defined as the last non-missing value prior to or on the day of randomisation, including unscheduled assessments that occur prior to the randomisation visit, for each subject and endpoint. If administration of the first dose of investigational product should happen to occur prior to randomisation, baseline will be defined as the last non-missing value on or before the day of the first dose.

For the Safety analysis set (SAS, see Section 4.1.2.1), baseline is defined as the last non-missing value prior to or on the day of first administration of IP, including unscheduled assessments that occur prior to the first dose visit, for each subject and endpoint.

If two assessments taken at the same day qualifie as baseline, the following will apply:

- If the variable is qualitative, then the worst value from a clinical perspective will be used as the baseline value.
- For KCCQ, the first assessment (value) will be used as baseline.
- For handling of cases when more than one value could qualify as baseline for any other reason, see Section 3.3.3.

3.3.1.2 Handling of incomplete dates

The following imputed dates will only be used for analysis purposes and will remain as reported (partially or completely missing) in subject listings.

Incomplete IP stop dates

Partially missing IP stop dates will be imputed as follows:

- If the day value of last dose is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of a known administration of IP, then this date will be used.

Incomplete adverse event dates

Partially or completely missing adverse event (AE) onset dates will be imputed as follows:

- If only the day value of the adverse event onset date is missing, the first day of the month will be used; unless this occurs in the same month and year as the latest of randomisation and date of first dose of IP, then the latest of randomisation and the date of first dose of IP will be used.
- If the day and month values of the adverse event onset date are missing, January 1 will be used; unless this occurs in the same year as the latest of randomisation and the date of first dose of IP, then the latest of randomisation and the date of first dose of IP will be used.
- If the adverse event onset date is completely missing, the latest of randomisation and the date of first dose of IP will be used.

Incomplete death dates

Partially or completely missing death dates will be imputed as follows:

- If only the day value of the death date is missing, the first day of the month will be used; unless this occurs in the same month and year as last visit date, the last visit date will be used.
- If the day and month values of the death date are missing, January 1 will be used; unless this occurs in the same year as last visit date, then last visit date will be used.
- If the death date is completely missing, last visit date will be used.

Incomplete efficacy event dates

Partially or completely missing event onset dates will be imputed as follows:

- If only the day value of the event onset date is missing, the first day of the month will be used; unless this occurs in the same month and year as randomisation, then the date of randomisation will be used.
- If the day and month values of the event onset date are missing, January 1 will be used; unless this occurs in the same year as randomisation, then the date of randomisation will be used.
- If the event onset date is completely missing, the date of randomisation will be used.

Incomplete concomitant medication dates

For medications that started prior to study start, start day will not be imputed. Partially or completely missing concomitant medication (CM) start dates will be imputed as follows:

- If only the day value of the CM start date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of randomisation, then the date randomisation will be used
- If the day and month values of the CM start date are missing, January 1 will be used; unless this occurs in the same year as the date of randomisation, then the date randomisation will be used.
- If the CM start date is completely missing, the date of randomisation will be used.

If medication is marked as 'Treatment continues' the stop date will not be imputed. Partially or completely missing CM stop dates (where applicable) will be imputed as follows:

- If only the day value of the CM stop date is missing, the last day of the month will be used; unless this occurs in the same month and year as the last visit, then the date of the last visit will be used.

- If the day and month values of the CM stop date are missing, December 31 will be used; unless this occurs in the same year as the last visit, then the date of the last visit will be used.

- If the CM stop date is completely missing, the date of the last visit will be used.

3.3.1.3 Laboratory data principles

Assessed values of the form '<x' (below the lower limit of quantification [LLoQ]) or '>x' (above the upper limit of quantification [ULoQ]) will be imputed as 'x/2' for '<x' and 'x' for '>x' in the calculations of summary statistics but displayed as '<x' or '>x' in listings. The number of imputations will be summarised. Missing safety laboratory data will not be imputed.

3.3.1.4 Study Day

Study Day will be calculated from the randomisation date and will be used to show start/stop day of assessments and events. Day 1 is the day of randomisation, Day -1 is the day prior to the date of randomisation, there is no Day 0.

- If the date of the event is on or after the randomisation date, then:
    - Study Day = date of event – date of randomisation + 1.
- If the date of the event is prior to the randomisation date, then:
    - Study Day = date of event – date of randomisation.

3.3.1.5 Study periods

Study periods for Full Analysis Set (FAS)

Screening period

The screening period starts at the date of signed informed consent and ends at the day before randomisation. For subjects enrolled but not randomised, the enrolment period ends at last visit.

Planned treatment period

The follow-up time for the Planned treatment period will be calculated from randomisation and to the earliest of day of visit 11 (if subject attended visit 11, otherwise day 343 will be used), date of withdrawal of consent or date of death. If withdrawal of consent or death did not occur, it

will be calculated from randomisation and to the earliest of day of visit 11 (if subject attended visit 11, otherwise day 343 will be used) or the last study visit.

Study periods for Safety Analysis Set (SAS)

Pre-treatment period

The pre-treatment period starts at the date of signed informed consent and ends before the date and timepoint of first dose of IP.

On-treatment period

The follow-up time for the On-treatment period will be calculated from the date of the first dose of IP and to the earliest of 14 days after last dose, date of withdrawal of consent or date of death. If withdrawal of consent or death did not occur, it will be calculated from the date of the first dose of IP and to the earliest of 14 days after last dose of study drug or the last study visit..

On-study period

The follow-up time for the On-study period will be calculated from the date of the first dose of IP and to the earliest date of withdrawal of consent or date of death. If withdrawal of consent or death did not occur, it will be calculated from the date of the first dose of IP and to the last study visit.

3.3.1.6 Subject terminology convention

The term "Participant" is generally used to refer to language based on the CSP, vendor technology, patient-reported outcomes (PROs), and publication titles. The word "subject" is more commonly encountered in the statistical sections of this SAP for consistency with standard statistical terminology. Participant, patient, and subject are used interchangeably.

3.3.1.7 Summary statistics

Quantitative data will be summarised by descriptive statistics including number of subjects in category (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Geometric mean and coefficient of variation (CV) will be calculated in addition to arithmetic mean and SD, if appropriate.

Categorical data will be summarised as the number and percentage of subjects in each treatment group for each category. When appropriate, number of missing observations will be presented, and these will not be included in the denominator when calculating percentages.

A general rule is to present descriptive summary statistics (mean, SD, median, Q1, Q3) to 1 more decimal place than the individual values. The minimum and maximum values will be reported to the same number of decimal places as the individual values.

Absolute change from baseline will be presented in addition to absolute values. It will be summarised by descriptive statistics at the same timepoints as absolute values, except for baseline itself.

All confidence intervals (CIs) will be 95%.

3.3.1.8 Time at risk and censoring

If a subject has an event with onset day during the study period being analysed (see Section 3.3.1.5), it will be included in the analysis. For subjects with an event, the time at risk will be derived as

- $Event\ onset\ date - date\ of\ randomisation + 1$ for FAS
- $Event\ onset\ date - date\ of\ first\ date\ of\ IP + 1$ for SAS

For event-free subjects, the time at risk will be derived based on the study period being analysed, see the definition in Section 3.3.1.5. Event-free subjects are censored on the last day of the study period.

3.3.1.9 Unit conventions

- 1 year is defined as 365.25 days
- 1 month is defined as 365.25/12 = 30.4375 days

3.3.2 Visit Window

Visit windows will be used for analysing visit-based data and are based on the target day for a scheduled visit, see Schedule of Activities in the CSP. The range of the windows for scheduled on-site assessments are shown in

Table 1.

The visit closest to the target day and within the visit window is assigned. This can be a scheduled or unscheduled assessment.

Table 1 Visit windows for on-site assessments

Scheduled assessment	Visit	Target Day	Visit window (days)
All endpoints			

Week 4	4	29	[2[1], 57]
Week 12	6	85	[58, 99]
Week 16	8	113	[100, 141]
Week 24	9	169	[142, 211]
Week 36	10	253	[212, 294]
Week 48	11	336	[295, 350]
Week 52	12	365	>350

[1] The Week 4 visit window also includes post-dose vital signs assessments (VS7) taken on the day of randomisation, but after the baseline assessment.

The analysis visit window as defined in Table 1 will not be used for the Orthostatic blood pressure test at 12 weeks. Instead, the nominal visit number will be used for this assessment.

Analysis visit windows for CCI will be described in Sections 4.2.9.4 and 4.2.18.1. Baseline is defined in Section 3.3.1.1.

3.3.3 Handling of Scheduled and Unscheduled Visits

Unscheduled visits can be assigned to a visit window if closer to the target day than the scheduled visit or if there is no measurement from a scheduled visit in the window. If a patient has performed more than one unscheduled visit within a window, the assessment closest to the target day will be used.

In case of ties between scheduled or unscheduled visits located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same day but different time), the value with the earlier entry time will be used.

In case of two or more scheduled or unscheduled visits for assessments with the same purpose and with identical dates and times (including possibly missing times), the average value will be derived, and in case that the record is assigned for its respective analysis visit, the average value will be used for analysis. This will be done both for cases with multiple baseline values or with multiple post-baseline values with the same date and time.

In some instances, several assessments of a vital sign variable are scheduled at the same visit for different purposes, e.g., systolic blood pressure at Visit 3. In this situation, the measurement from

the assessment for only vital signs purposes would be used, unless this is missing. If it is missing, then the supine BP pre-orthostatic test measurement or the supine BP pre-6MWT would be used for the analysis (in that order).

3.3.4 Multiplicity/Multiple Comparisons

The formal hypotheses tests will address the treatment effect of AZD4831 versus placebo on the dual primary endpoints KCCQ Total symptom score (TSS) change from baseline at 16 weeks and 6-minute walk distance (6MWD) change from baseline at 16 weeks. Multiplicity across primary and secondary endpoints due to multiple tests will be accounted for according to a gatekeeping test strategy for alpha recycling. The strategy is applied to control the family-wise type I error rate of 5 % of an erroneous rejection of the null hypothesis (Burman, 2009) (FDA, 2017).

The comparison between pooled doses of AZD4831 and placebo is formally tested, unless the randomisation to the AZD4831 5mg treatment group is stopped during the study, in which case the comparison of AZD4831 2.5mg and placebo will be formally tested.

First, both dual primary endpoints are tested with Holm method. The p-values for KCCQ-TSS and 6MWD are sorted from lowest to highest, if the lowest p-value is rejected at $\alpha/2 = 0.025$, then the other endpoint is tested at full $\alpha = 0.05$. If both dual primary endpoints are rejected, then the full testing mass of 0.05 will be passed on to testing in the secondary endpoint family.

The secondary endpoint family will be tested within a fixed sequence in the order listed below:

1. KCCQ-TSS change from baseline at 24 weeks
2. KCCQ-TSS change from baseline at 48 weeks
3. 6MWD change from baseline at 24 weeks
4. 6MWD change from baseline at 48 weeks
5. Change from baseline in log-transformed NT-proBNP at 16 weeks
6. Change from baseline in log-transformed NT-proBNP at 24 weeks
7. Change from baseline in log-transformed NT-proBNP at 48 weeks
8. LV-GLS change from baseline at 16 weeks
9. LV-GLS change from baseline at 24 weeks

10. LAVI change from baseline at 16 weeks
11. LAVI change from baseline at 24 weeks
12. LVMI change from baseline at 16 weeks
13. LVMI change from baseline at 24 weeks
14. Change from baseline in log-transformed hsCRP at 16 weeks
15. Change from baseline in log-transformed hsCRP at 24 weeks
16. Change from baseline in log-transformed hsCRP at 48 weeks
17. Change from baseline in log-transformed IL-6 at 16 weeks
18. Change from baseline in log-transformed IL-6 at 24 weeks
19. Change from baseline in log-transformed IL-6 at 48 weeks

By this approach, full alpha is passed onto the next hypothesis in the sequence until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected. P-values from all endpoints in the hierarchy below the first non-rejected secondary endpoint and explorative endpoints are not adjusted, thus will be nominal and considered explorative.

3.3.5 Handling of Protocol Deviations in Study Analysis

The definition and handling of important protocol deviations (IPDs) are presented in a separate Protocol Deviation Plan. Definition and presentation of protocol deviations are described in Section 4.1.5.

3.3.5.1 Covid-19

The impact of the Covid-19 pandemic is captured in exposure, disposition and visit data case report form pages as a general question on whether administration/subject's status/visit was impacted by any global/country situation. Subjects affected by the COVID-19 pandemic, such as efficacy and safety assessments not per CSP, will be recorded as protocol deviations. Listings of COVID-19 study disruptions and number of subject dispositions due to COVID-19 will be presented.

4 STATISTICAL ANALYSIS

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical and surgical history, use of prior and concomitant medication, and study drug compliance.

The tables will be presented by AZD4831 2.5mg, AZD4831 5mg, AZD4831 Total (pooled treatment groups AZD4831 2.5mg and 5mg), placebo and Total.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Screened subjects

Enrolled subjects who have signed the informed consent form (ICF) of the study.

Randomised subjects

Subjects who have been randomised to one of the treatment groups.

Subjects who started treatment

Subjects who have received at least one dose of IP.

Subjects who completed treatment

Subjects who have an assessment on or after Week 48 without discontinuing study medication prior to the visit. A subject who dies during the study without having permanently discontinued IP prior to date of death, is considered to have completed treatment.

Subjects who discontinued treatment

Subjects who have permanently prematurely discontinued IP.

Subjects who completed study

Subjects who have completed the last protocol specified visit/assessment (including telephone contact) regardless of the number of doses of study medication they have received.

Subjects withdrawn from study

Subjects who have withdrawn consent or been lost to follow-up.

Subjects who discontinued treatment due to global/country situation

Subjects who have permanently prematurely discontinued IP due to global/country situation(s).

Subjects who withdraw from study due to global/country situation
Subjects who have withdrawn consent, been lost to follow-up, or died, due to global/country situation(s).

4.1.1.2 Presentation
Disposition of all subjects will be presented, from screening to study completion. The number of enrolled and screen-failed subjects (and reason) will be summarised. The number and percentage of subjects will be presented by treatment group and in total for all subjects in the following categories:

- screened,
- screen failures by reason,
- randomised,
- did not receive IP by reason,
- started treatment,
- completed treatment,
- discontinued treatment (and reason),
- completed study (with subcategories alive and dead),
- withdrawn from study by reason,

In addition, number and percentage of subjects who discontinued treatment due to global/country situation and subjects who withdraw from study due to global/country situation will be tabulated separately.

Listings
A listing of screen failures and subjects discontinued from study will be presented.

4.1.2 Analysis Sets
4.1.2.1 Definitions and Derivations
Full analysis set
All subjects who have been randomised to study treatment and who have received at least one dose of investigational product will be included in FAS irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed according to their randomised

study medication assignment, irrespective of the treatment actually received. FAS is considered the primary analysis set for the primary and secondary efficacy variables as well as for the exploratory efficacy variables.

Safety analysis set

SAS consists of all subjects who have received at least one dose of IP. Erroneously treated subjects (e.g., those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A subject who has received any dose of the active IP will be classified as in the active IP treatment group. A subject who has received both doses of active IP will be classified as in the highest dose treatment group. SAS is used for all safety analyses.

4.1.2.2 Presentation

Analysis sets will be presented by number of subjects in each set for all randomised subjects, by treatment group and total number of subjects. The reason for exclusion from an analysis set will be presented.

Listings

A listing of subjects excluded from an analysis set will be presented along with reasons for exclusion.

4.1.3 Study Recruitment

4.1.3.1 Definitions and Derivations

The regions are defined as Europe, where Western Europe and Eastern Europe are subsets, North America, South America, Australia and Asia, each region including the following countries:

- Europe: Belgium, Bulgaria, Czech Republic, Denmark, France, Hungary, Netherlands, Poland, Russia, Slovakia, Sweden, Turkey.
    - West Europe: Belgium, Denmark, France, Netherlands, Sweden.
    - East Europe: Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey
- North America: Canada, USA.
- South America: Brazil.
- Asia and Australia: Australia, Japan, Taiwan.

4.1.3.2 Presentation

The number of subjects recruited by region, country and site will be presented, by treatment group and total number of subjects for each analysis set and screened subjects.

4.1.4 Stratification factors

4.1.4.1 Definitions and Derivations

The randomisation will be stratified by Neutrophil count as

- $>4 \times 10^6$/mL
- $\leq 4 \times 10^6$/mL.

4.1.4.2 Presentation

The number and percentage of subject in each stratum will be presented by treatment group for FAS, as recorded in the Interactive response technology (IRT).

4.1.5 Protocol Deviations

4.1.5.1 Definitions and Derivations

Important protocol deviations (IPD) are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety, or well-being. The IPDs are related to

- Inclusion criteria
- Exclusion criteria
- Discontinuation criteria for study product met but subject not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study
- IP deviations
- Excluded medication taken
- Deviations related to study procedure
- Other important deviations.

All IPDs except for dosing error will be identified and documented by the study team prior to unblinding of the trial. Details on the handling of IPDs are specified in the Protocol deviation plan.

Listings
A listing of subjects with important protocol deviations will be presented.

4.1.5.2 Presentation
The number and percentage of subjects with at least one IPD category as well as the number and percentage of subjects meeting each IPD category will be provided by treatment group and in total. Subjects meeting an IPD category more than once will be counted once for the corresponding IPD category. Any subject who has more than one IPD category will be counted once in the overall summary. IPDs will not be used to exclude any subject from any analysis set, nor to exclude any data from subjects included in an analysis set. Subjects having IPDs will be summarised for the FAS population by treatment group and in total.

4.1.6 Demographics
4.1.6.1 Definitions and Derivations
Demographic characteristics includes

- Age (years)
- Age group (<65; 65-75; >75 years)
- Sex (male, female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity
    - Hispanic
    - Not Hispanic
- Ethnic Asian subgroup (triggered by ‘Asian’ in the RSG field for ethnic origin in the CRF):
    - Asian, not specified
    - Chinese

- Japanese
- Taiwanese
- Korean
- Vietnamese
- Other

4.1.6.2 Presentation

Demographic characteristics will be summarised for the FAS population by treatment group and in total.

Listings

A listing of demographics and baseline characteristics for randomised subjects will be presented.

4.1.7 Baseline Characteristics

4.1.7.1 Definitions and Derivations

Baseline subject characteristics includes

- Height (cm)
- Weight (kg)
- Body mass index, calculated using weight and height variables at baseline (kg/m^2)
- Categorical body mass index (<30, ≥ 30 and <40, ≥ 40) (kg/m^2)

4.1.7.2 Presentation

Baseline subject characteristics will be summarised for the FAS population by treatment group and in total.

4.1.8 Alcohol and nicotine use at baseline

4.1.8.1 Definitions and Derivations

Alcohol use and Nicotine use are categorised as

- Never
- Former

- Current

4.1.8.2 Presentation

Alcohol use and Nicotine use will be presented by number of subjects in each category for the FAS population by treatment group and in total.

4.1.9 Baseline Disease Characteristics

4.1.9.1 Definitions and Derivations

The following disease characteristics will be presented at baseline:

- KCCQ-TSS (points)
- Categorical KCCQ-TSS (≤80, >80) (points)
- KCCQ Overall summary score (OSS) (points)
- Categorical KCCQ-OSS (≤80, >80 and ≤90, >90) (points)
- 6MWD (meters)
- Categorical 6MWD (≤350, >350 and ≤400, >400) (meters)
- Hospitalised for HF prior to randomisation (Yes/No)
- Time from prior hospitalisation for HF to randomisation (months) (for subjects with prior hospitalisation)
- NYHA classification (II, III, IV)
- LVEF (%)
- Categorical LVEF (%) (<50, ≥50)
- History of atrial fibrillation (Yes/No)
- History of atrial flutter (Yes/No)
- History of hypertension (Yes/No)
- NT-proBNP (pg/mL)
- Neutrophil count (10^9/L)

- Neutrophil count category (10^9/L) (≤4, >4)
- eGFR, calculated according to CKD-EPI S-Creatinine equation (mL/min/1.73m^2)
- Categorical eGFR, calculated according to CKD-EPI equation 60, >60) (mL/min/1.73m^2)

For baseline eGFR, age at screening is used.

4.1.9.2 Presentation

Baseline disease characteristics will be summarised for the FAS population by treatment group and in total.

4.1.10 Medical History and Concomitant Disease

4.1.10.1 Definitions and Derivations

Disease related medical history and surgical/procedure history will be coded according to MedDRA.

4.1.10.2 Presentation

Medical history and concomitant disease will be presented for FAS, by treatment group and in total, classified by System organ class (SOC) and Preferred term (PT). Percentages will be calculated with number of subjects in FAS as denominator. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of that SOC/PT. Relevant medical and surgical/procedure history will be sorted by international order of SOC and alphabetically by PT.

4.1.11 Prior and Concomitant Medications

4.1.11.1 Definitions and Derivations

Prior medication is defined as any medication taken by the subject before the first dose of study medication. If the end date is before or on the day of first dose of study medication, it will be defined as a prior medication.

Concomitant therapy is defined as any medication or vaccine taken concurrently with study medication regardless of the start date of the medication. If a medication starts on or prior to last dose + 14 days, it is considered to be taken concomitantly. If the end date of the medication is prior to or on the day of first dose the medication will not be considered to be taken concomitantly.

Allowed and prohibited and/or restricted concomitant medications will be presented respectively. Section 6.5 of the CSP lists medications and treatments which are prohibited and/or restricted. All other concomitant medications are classified as allowed.

All medications will be reported by ATC classification and generic drug name and are coded using the latest version of WHO Drug Dictionary (WHODD).

4.1.11.2 Presentation

Number of subjects that have taken prior and concomitant medications will be presented for FAS, by treatment group and in total, classified by ATC classification and generic drug name, and are coded using the latest version of WHO Drug Dictionary (WHODD). Percentages will be calculated with number of subjects in FAS as denominator. Subjects are only counted once per ATC classification and generic drug name regardless of the number of medications within each category. Generic drug name will be presented nested within the relevant ATC classification and sorted alphabetically by ATC classification and then generic drug name.

Prior medications, disallowed concomitant medications and allowed concomitant medications will be presented separately.

Listings

A listing of any concomitant medication for randomised subjects will be presented.

4.1.12 Study Drug Compliance

4.1.12.1 Definitions and Derivations

Compliance with study medication is defined as the number of received doses, divided by the number of expected doses, multiplied by 100, expressed as a percentage. The number of received doses is defined as the pill count difference between pills dispensed and pills returned.

The number of expected doses is defined as the number of expected doses between first dose and time of last dose according to CSP or the time when study medication is prematurely permanently discontinued. If the number of tablets dispensed or the number of tablets returned is missing for at least 1 observation, compliance is not calculated for that subject.

The level of compliance of IP per subject will be categorised as

- <80%,
- 80%-120%, and
- >120%.

4.1.12.2 Presentation

Study drug compliance will be presented descriptively, including mean, SD, median, Q1, Q3, minimum, maximum, and 5% and 95% percentiles and categorically by compliance group

(<80%, 80%-120%, >120%) for SAS by treatment group and in total. Number of subjects with missing compliance will be presented.

Listings

A listing of administration and compliance of IP will be presented.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and exploratory endpoints including sensitivity and supportive analyses.

Primary estimand

The primary estimand is defined by the following attributes:

- **Endpoint:** Change from baseline in variable at analysis timepoint.
- **Treatment:** Randomised treatment group (regardless of actual received treatment), AZD4831 2.5mg/5mg or placebo, administered in addition to optimal background therapy for co-morbidities.
- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF and alive. This is implemented on evaluable subjects defined by a subset of FAS (see Table 2) which have available measurements of the efficacy endpoints at baseline and analysis timepoint.
- **Population-level summary:** Difference in adjusted mean change from baseline to analysis timepoint or adjusted geometric mean ratio.
- **Handling of intercurrent events:** Treatment policy strategy combined with principal stratum strategy
    - Initiation or change of concomitant medication and permanent premature discontinuations of IP will be handled by a treatment policy strategy, i.e., ignoring these intercurrent events, implemented by including all available data.
    - Subjects with intercurrent events resulting in missing assessments of the primary endpoints, e.g., terminal events or withdrawal from the study, are expected to be very few and will be excluded from the analysis (principal stratum strategy).

Supplementary estimands

Supplementary analyses of the primary objectives will be conducted using four different supplementary estimands. The treatment attribute for the supplementary estimands is the same as for the primary estimand.

For the first supplementary estimand, the other attributes are the following:

- **Endpoint:** Change from baseline in variable at analysis timepoint.
- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF. Implemented by FAS.
- **Population-level summary:** Difference in adjusted mean change from baseline to analysis timepoint.
- **Handling of intercurrent events:** Treatment policy strategy combined with hypothetical strategy
    - Initiation or change of concomitant medication and permanent premature discontinuations of IP will be handled by a treatment policy strategy, i.e., ignoring these intercurrent events, implemented by including all available data.
    - Deaths will be handled by a hypothetical strategy for the hypothetical scenario where death cannot occur. Under the assumption that death is a non-informative event, this is implemented by including all available data up to time of death.

For the second supplementary estimand, the other attributes are the following:

- **Endpoint:** Change from baseline in variable at analysis timepoint with death considered worst possible outcome.
- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF. Implemented by FAS.
- **Population-level summary:** Difference in adjusted median change from baseline to analysis timepoint.

- **Handling of intercurrent events:** Treatment policy strategy combined with composite variable strategy.
    - Initiation or change of concomitant medication and permanent premature discontinuations of IP will be handled by a treatment policy strategy, i.e., ignoring these intercurrent events, implemented by including all available data.
    - Death is handled by incorporating this intercurrent event in the endpoint and consider it as worst possible outcome (composite variable strategy).
    - Subjects with intercurrent events resulting in missing assessments of the primary endpoints other than death are expected to be very few and will be excluded from the analysis (principal stratum strategy).

For the third supplementary estimand, the other attributes are the following:

- **Endpoint:** Change from baseline in variable at analysis timepoint.
- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF who are alive and have not permanently prematurely discontinued IP. This is implemented on evaluable subjects defined by a subset of FAS which have not discontinued IP and have available measurements of the efficacy endpoints at baseline and analysis timepoint.
- **Population-level summary:** Difference in adjusted mean change from baseline to analysis timepoint or adjusted geometric mean ratio.
- **Handling of intercurrent events:** Treatment policy strategy combined with principal stratum strategy.
    - Initiation or change of concomitant medication will be handled by a treatment policy strategy, i.e., ignoring these intercurrent events. Implemented by including all available data.
    - Subjects with intercurrent events resulting in missing assessments of the primary endpoints, e.g., terminal events or withdrawal from the study, are expected to be very few and will be excluded from the analysis (principal stratum strategy).

- Subjects who have discontinued IP will be excluded from the analysis (principal stratum strategy).

For the fourth supplementary estimand, the other attributes are the following:

- **Endpoint:** Change from baseline in variable at analysis timepoint.
- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF. This is implemented on evaluable subjects defined by a subset of FAS (see Table 2) which have available measurements of the efficacy endpoints at baseline and analysis timepoint.
- **Population-level summary**: Difference in adjusted mean change from baseline to analysis timepoint or prior to death, if earlier, as a function of baseline.
- **Handling of intercurrent events:** Treatment policy strategy combined with while-alive strategy and principal stratum strategy
  - Initiation or change of concomitant medication and permanent premature discontinuations of IP will be handled by a treatment policy strategy, i.e., ignoring these intercurrent event, implemented by including all available data.
  - Deaths will be handled by a while-alive strategy, implemented by including the last available efficacy assessment in the analysis.
  - Subjects with intercurrent events resulting in missing assessments of the primary endpoints other than death are expected to be very few and will be excluded from the analysis (principal stratum strategy).

Table 2 Overview of efficacy objectives, endpoints and estimands

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Objective 1: To evaluate the effect of AZD4831 on KCCQ-TSS					
Primary analysis of primary endpoint targeting	KCCQ-TSS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.1.4

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
primary estimand					
Sensitivity analysis of primary endpoint targeting the primary estimand	KCCQ-TSS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.1.5
Supplementary analysis of primary endpoint targeting first supplementary estimand	KCCQ-TSS change from baseline at 16 weeks	FAS	Treatment policy strategy combined with hypothetical strategy	Difference in adjusted mean change from baseline at 16 weeks (MMRM)	4.2.1.6
Supplementary analysis of primary endpoint targeting second supplementary estimand	Composite of KCCQ-TSS change from baseline at 16 weeks and death	FAS	Treatment policy strategy combined with composite strategy	Difference in adjusted median change from baseline at 16 weeks (Rank ANCOVA and Hodges-Lehmann)	4.2.1.6
Supplementary analysis of primary endpoint targeting third supplementary estimand	KCCQ-TSS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.1.6
Supplementary analysis of primary endpoint targeting fourth supplementary estimand	KCCQ-TSS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with while-alive strategy and principal stratum strategy	Difference in adjusted mean change from baseline to analysis timepoint or prior to death, if earlier, as a function of baseline	4.2.1.6
Subgroup analysis of primary endpoint targeting primary estimand	KCCQ-TSS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.1.7
Objective 2: To evaluate the effect of AZD4831 on 6MWD					

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Primary analysis of primary endpoint targeting primary estimand	6MWD change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.2.4
Sensitivity analysis of primary endpoint targeting the primary estimand	6MWD change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.2.5
Supplementary analysis of primary endpoint targeting first supplementary estimand	6MWD change from baseline at 16 weeks	FAS	Treatment policy strategy combined with hypothetical strategy	Difference in adjusted mean change from baseline at 16 weeks (MMRM)	4.2.2.6
Supplementary analysis of primary endpoint targeting second supplementary estimand	Composite of KCCQ-TSS change from baseline at 16 weeks and death	FAS	Treatment policy strategy combined with composite strategy	Difference in adjusted median change from baseline at 16 weeks (Rank ANCOVA and Hodges-Lehmann)	4.2.2.6
Supplementary analysis of primary endpoint targeting third supplementary estimand	6MWD change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.2.6
Supplementary analysis of primary endpoint targeting fourth supplementary estimand	6MWD change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with while-alive strategy and principal stratum strategy	Difference in adjusted mean change from baseline to analysis timepoint or prior to death	4.2.2.6
Subgroup analysis of primary endpoint targeting	6MWD change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.2.7

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
primary estimand			principal stratum strategy		
Objective 3: To evaluate the effect of AZD4831 on KCCQ-TSS					
Primary analysis of secondary endpoints targeting primary estimand	KCCQ-TSS change from baseline at 24 and 48 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 24 and 48 weeks (ANCOVA)	4.2.3.4
Objective 4: To evaluate the effect of AZD4831 on 6MWD					
Primary analysis of secondary endpoints targeting primary estimand	6MWD change from baseline at 24 and 48 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 24 and 48 weeks (ANCOVA)	4.2.4.4
Objective 5: To evaluate the effect of AZD4831 on NT-proBNP					
Primary analysis of secondary endpoints targeting primary estimand	Change from baseline in log-transformed NT-proBNP at 16, 24 and 48 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.5.4
Supplementary analysis of secondary endpoint targeting third supplementary estimand	Change from baseline in log-transformed NT-proBNP at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.5.5
Subgroup analysis of secondary endpoint targeting primary estimand	Change from baseline in log-transformed NT-proBNP at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.5.6
Objective 6: To evaluate the effect of AZD4831 on echocardiographic parameter LV-GLS					

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Primary analysis of secondary endpoints targeting primary estimand	LV-GLS change from baseline at 16 and 24 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 and 24 weeks (ANCOVA)	4.2.6.4
Supplementary analysis of secondary endpoints targeting third supplementary estimand	LV-GLS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.5
Subgroup analysis of secondary endpoint targeting primary estimand	LV-GLS change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.6
Objective 7: To evaluate the effect of AZD4831 on echocardiographic parameter LAVI					
Primary analysis of secondary endpoints targeting primary estimand	LAVI change from baseline at 16 and 24 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 and 24 weeks (ANCOVA)	4.2.6.4
Supplementary analysis of secondary endpoints targeting third supplementary estimand	LAVI change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.5
Subgroup analysis of secondary endpoint targeting primary estimand	LAVI change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.6

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Objective 8: To evaluate the effect of AZD4831 on echocardiographic parameter LVMI					
Primary analysis of secondary endpoints targeting primary estimand	LVMI change from baseline at 16 and 24 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 and 24 weeks (ANCOVA),	4.2.6.4
Supplementary analysis of secondary endpoints targeting third supplementary estimand	LVMI change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.5
Subgroup analysis of secondary endpoint targeting primary estimand	LVMI change from baseline at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Difference in adjusted mean change from baseline at 16 weeks (ANCOVA)	4.2.6.6
Objective 9: To assess the pharmacokinetics of AZD4831					
Primary analysis of secondary endpoints targeting primary estimand	Plasma Concentrations of AZD4831	SAS	Treatment policy strategy	Summary statistics	4.2.7.4
Objective 10: To evaluate the effect of AZD4831 on inflammatory biomarkers					
Primary analysis of secondary endpoints targeting primary estimand	Change from baseline in log-transformed hsCRP and IL-6 at 16, 24, and 48 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.8.4
Supplementary analysis of secondary endpoint targeting third	Change from baseline in log-transformed IL-6 at 16 weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.8.5

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
supplementary estimand					
Subgroup analysis of secondary endpoint targeting primary estimand	Change from baseline in log-transformed hsCRP and IL-6 at 16weeks	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	Adjusted geometric mean ratio between baseline and 16, 24 and 48 weeks (ANCOVA)	4.2.8.6
Objective 11: To evaluate the effect of AZD4831 on CCI					
CCI		Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI	4.2.9.4
Objective 20: To determine whether AZD4831 is superior to placebo CCI					
Primary analysis of exploratory endpoints targeting primary estimand	CCI	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI	4.2.10.4
Objective 12: To evaluate the effect of AZD4831 on CCI					

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Primary analysis of exploratory endpoints targeting primary estimand	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI [redacted]	4.2.11.4
CCI [redacted] on aspects of the 6MWT, other than the 6MWD					
Primary analysis of exploratory endpoints targeting primary estimand	CCI [redacted]	FAS	Treatment policy strategy	CCI [redacted]	4.2.12.3
Objective 14: To evaluate the effect of AZD4831 CCI [redacted]					
Primary analysis of exploratory endpoint targeting primary estimand	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI [redacted]	4.2.13.4
Objective 15: To evaluate the effect of AZD4831 on CCI [redacted]					
Primary analysis of exploratory endpoints targeting primary estimand	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI [redacted]	4.2.14.4
Objective 16: To evaluate the effect of AZD4831 on echocardiographic parameter E/e'					
Primary analysis of exploratory endpoints targeting primary estimand	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI [redacted]	4.2.15.4
Objective 17: To evaluate the effect of AZD4831 on cardiovascular events					

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
Primary analysis of exploratory endpoints targeting time-to-event estimand	Composite of HF hospitalisation, urgent HF visits with requirement for additional loop diuretic treatment, MI, cardiovascular deaths, and all-cause mortality from baseline at end of study	FAS	Treatment policy strategy combined with composite strategy	Kaplan-Meier % difference, Hazard ratio	4.2.16.4
Objective 18: CCI [redacted]					
Primary analysis of exploratory endpoints targeting primary estimand	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	CCI [redacted]	4.2.17.4
Objective 19: To evaluate if the CCI [redacted]					
Primary analysis of exploratory endpoints targeting	CCI [redacted]	Principal stratum of FAS	Treatment policy strategy combined with	CCI [redacted]	4.2.18.4

Statistical category	Endpoint	Population	Handling of intercurrent events	Population level summary (analysis)	Details in section
primary estimand			principal stratum strategy		
Objective 21: To evaluate the[redacted]					
Primary analysis of exploratory endpoints targeting primary estimand	[redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	[redacted]	4.2.19.4
Objective 22: To evaluate the[redacted]					
Primary analysis of exploratory endpoints targeting primary estimand	[redacted]	Principal stratum of FAS	Treatment policy strategy combined with principal stratum strategy	[redacted]	4.2.20.4

FAS Full analysis set; SAS Safety analysis set

4.2.1 Primary Endpoint – KCCQ-TSS change from baseline at 16 weeks

4.2.1.1 Definition

One of the dual primary efficacy endpoints is KCCQ-TSS change from baseline at 16 weeks. The primary, sensitivity and subgroup analyses for this endpoint will be evaluated under the primary estimand defined in Section 4.2.

4.2.1.2 Derivations

The KCCQ-TSS variable incorporates the Symptoms frequency and the Symptoms burden domains of the KCCQ (Gasparyan, 2020). Results for each domain are summarised and transformed to a score of 0 to 100 where a higher score indicates a better health status.

Each response to a KCCQ question is assigned an ordinal value.

For Symptoms frequency, the response will be assigned a value starting from 1 (most frequent) to 5 or 7 (least frequent), depending on the number of options. The score for each question will be derived as

$$(\text{score from question} - 1)/(\text{number of unique ordinal value options} - 1).$$

If responses to at least two of the Symptoms frequency questions are not missing, the Symptoms frequency score is calculated as

$$100 * \text{mean}(\text{scores for all Symptoms frequency questions}).$$

For Symptoms burden, the response will be assigned a score starting from 1 (most bothersome) to 5 (not bothersome). If response to at least one of the Symptoms burden questions are not missing, the Symptoms burden score is calculated as

$$100 * (\text{mean of scores for all Symptoms burden questions actually answered} - 1)/4.$$

KCCQ-TSS is derived as the mean of the Symptoms frequency score and Symptoms burden score.

The absolute change from baseline at 16 weeks will be derived.

4.2.1.3 Handling of Dropouts and Missing Data

For the primary and supplementary analyses using ANCOVA as estimator, missing data will not be imputed. Subjects with missing baseline data of any variables which are used as covariates in the analysis will be excluded from these analyses. For the supplementary analysis using MMRM as estimator all available data will be included.

4.2.1.4 Primary Analysis of Primary Endpoint

The KCCQ-TSS change from baseline at 16 weeks endpoint is analysed under the primary estimand using ANCOVA as primary estimator, comparing AZD4831 Total versus placebo. The individual doses will also be compared separately with placebo but are not part of the formal testing sequence.

Treatment group and neutrophil count stratum are included as categorical covariates and baseline value of respective endpoint as continuous covariate. Subjects with available data at the 16 weeks analysis timepoint will be included in the analysis.

The difference in mean change from baseline for the primary efficacy endpoints will be evaluated to test the following hypotheses:

H0: μ(AZD4831 Total) - μ(placebo) = 0, versus the alternative hypothesis:

H1: μ(AZD4831 Total) - μ(placebo) ≠ 0, where μ(x) is true mean change from baseline for treatment x.

The strategy to control for multiplicity is defined in Section 3.3.4:

Presentation
Least squares mean estimates for each treatment group and the difference in least squares means between active treatment groups and placebo with 95% CIs and p-values will be presented.

Distributions of endpoint data will be presented by summary statistics over time, probability density function (PDF) curves and empirical cumulative distribution function (eCDF) curves, by treatment group.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

As a sensitivity analysis the primary endpoint will be analysed using an ANCOVA with treatment group included as categorical covariate and neutrophil count and baseline value as continuous covariates. The analysis is evaluated under the primary estimand defined in Section 4.2.

Presentation
See Section 4.2.1.4. Nominal p-value will be presented.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

A mixed model repeated measures (MMRM) model is used as one of the supplementary estimators for the KCCQ-TSS change from baseline at 16 weeks endpoint, comparing AZD4831 versus placebo. This analysis is evaluated under the first supplementary estimand defined in Section 4.2.

Treatment group, neutrophil count stratum, visit and treatment-by-visit interaction term are included as fixed effects and continuous baseline value of respective endpoint as covariate. The covariance structure used is unstructured (UN). If the model does not converge with UN, then autoregressive order 1 (AR [1]) and heterogeneous autoregressive order 1 (ARH [1]) structures will be tried in this order. The final covariance structure will be decided based on model convergence status.

A second supplementary analysis will be evaluated under the second supplementary estimand defined in Section 4.2. The ranked change from baseline for KCCQ-TSS at 16 weeks will be assessed. For this estimand, there are two estimators: a stratified rank ANCOVA and Hodges Lehmann location-shift estimates.

A two-sided nominal p-value will be derived from a stratified rank ANCOVA, testing the equality of distributions of ranked outcomes between AZD4831 Total and placebo. First the change from baseline at week 16 in each of the primary efficacy endpoints as well as values of the baseline covariate will be transformed to standardised ranks within each neutrophil count randomisation stratum, using fractional ranks (dividing by the denominator n+1) and the mean method for ties. Within each stratum, diseased subjects are ranked worse than any alive subject. Within the group of diseased subjects for each stratum, subjects are ranked based on their last endpoint value while alive. Separate ANCOVA models will be fitted to the ranked data for each randomisation stratum using a regression model with the ranked composite endpoint as the dependent variable, adjusting for the ranked baseline as a covariate. Residuals from this regression model will be captured for testing of differences between treatment groups. The Cochran-Mantel-Haenszel (CMH) test, stratified by neutrophil count randomisation stratum, using the values of the residuals as scores will be used to compare treatment groups.

Hodges-Lehmann estimates will be used to estimate the treatment effect in terms of location-shift, i.e., the difference in population medians between active and placebo arm.

A third supplementary analysis will be evaluated under the third supplementary estimand defined in Section 4.2 using ANCOVA as primary estimator, comparing AZD4831 versus placebo. Treatment group and neutrophil count stratum are included as categorical covariates and baseline value of respective endpoint as continuous covariate. Subjects with available data and who have not discontinued IP at the 16 weeks analysis timepoint will be included in the analysis.

A fourth supplementary analysis will be evaluated under the fourth supplementary estimand defined in Section 4.2 using ANCOVA as primary estimator, comparing AZD4831 versus placebo. Treatment group and neutrophil count stratum are included as categorical covariates, the baseline value of respective endpoint as continuous covariate and a term for baseline-by-treatment interaction. Subjects with available data at baseline and analysis timepoint or who have died prior to the analysis timepoint will be included in the analysis.

Presentation

For the MMRM analysis, see presentation part of Section 4.2.1.4. Nominal p-values will be presented.

For the rank ANCOVA and Hodges Lehmann analysis, median estimates for each treatment group and the difference in medians between active treatment groups and placebo with 95% CIs and nominal p-values will be presented.

For the third supplementary analysis, see presentation part of Section 4.2.1.4. Nominal p-values will be presented.

For the fourth supplementary analysis of KCCQ-TSS, least squares mean estimates are evaluated at a baseline value of 60 points. Least squares mean estimates for each treatment group and the difference in least squares means between active treatment groups and placebo with 95% CIs and nominal p-values will be presented. In addition, parameter estimates from the ANCOVA model will be tabulated with standard errors and nominal p-value and the difference between the two regression lines versus the baseline values will be presented in a figure.

4.2.1.7 Subgroup Analyses

A subgroup analysis will be conducted for this endpoint under the primary estimand defined in Section 4.2. For each of the pre-specified subgroup variables, a separate ANCOVA model will be fitted using the same terms as used in the primary analysis in Section 4.2.1.4 and additionally including the subgroup variable and the interaction term for subgroup-by-treatment interaction.

Subgroups

The subgroup analyses will be performed for the following baseline and demographic variables and categorisations. The cut-off values are based on baseline values.

- Age (<65; 65-75; >75 years)
- Sex (Male, Female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Hispanic/Latino (Yes/No)
- Geographic region (Europe, North America, South America, Asia and Australia) with regions defined as in Section 4.1.3.
- BMI (<30, ≥30)
- Alcohol consumption (Never, Former, Current)
- Nicotine consumption (Never, Former, Current)
- KCCQ-TSS (points) (≤80, >80)
- 6MWD (meters) (≤350, >350)
- Hospitalized for HF prior to randomisation (Yes/No)

- NYHA functional classification (II, III, IV)
- LVEF (%) (<50, ≥50)
- History of atrial fibrillation (Yes/No)
- History of atrial flutter (Yes/No)
- History of hypertension (Yes/No)
- NT-proBNP (≤Median, >Median)
- Neutrophil count (≤4 $\times 10^9$/L, >4 $\times 10^9$/L)
- HbA1C (%) (<6.5, ≥6.5)
- eGFR, calculated according to CKD-EPI S-Creatinine equation (mL/min/1.73m^2) (≤60, >60)
- S-Cystatin C (≤Median, >Median)
- MPO levels (≤Median, >Median)
- Urinary albumin-to-creatinine ratio (UACR) (≤Median, >Median)
- Ceruloplasmin (≤Median, >Median)
- Iron deficiency determined by Serum Ferritin in combination with Transferrin saturation (Serum Ferritin <100ng/mL OR Serum Ferritin 100-299 ng/mL with Transferrin saturation <20%) (Yes/No)
- Red cell distribution width (%) (≤14, >14)
- Hepcidin (≤Median, >Median)
- hsCRP (≤Median, >Median)

Transferrin saturation is derived as S-Iron/TIBC * 100. See Section 4.2.17.2 for derivation of UACR.

Presentation

See presentation part of Section 4.2.1.4, however the p-value for each subgroup will be excluded. In addition, p-value of interaction will be presented for each subgroup. A forest plot will be

presented for difference in least squares means with 95% CIs. If any category of a subgroup variable contains less than 5% of the subjects in the full analysis set, separate ANCOVA models similar to the overall analysis will instead be fitted to subjects in each separate category, thus no p-value of interaction will be presented.

4.2.2 Primary Endpoint – 6MWD change from baseline at 16 weeks

4.2.2.1 Definition

The other dual primary efficacy endpoint is 6MWD change from baseline at 16 weeks. For this endpoint, the same estimands will be used as for the analysis of KCCQ-TSS change from baseline at 16 weeks described in Sections 4.2 and 4.2.1.

4.2.2.2 Derivations

The absolute change from baseline at 16 weeks will be derived.

4.2.2.3 Handling of Dropouts and Missing Data

See Section 4.2.1.3 for details.

4.2.2.4 Primary Analysis of Primary Endpoint

See section 4.2.1.4 for details.

4.2.2.5 Sensitivity Analyses of the Primary Endpoint

See Section 4.2.1.5 for details.

4.2.2.6 Supplementary Analyses of the Primary Endpoint

See Section 4.2.1.6 for details. For the fourth supplementary analysis, the ANCOVA model will include treatment group and neutrophil count stratum as categorical covariates, and the baseline value as continuous covariate. The figure described for the KCCQ-TSS fourth supplementary analysis in Section 4.2.1.6 will not be presented for this analysis.

4.2.2.7 Subgroup Analyses

See Section 4.2.1.7 for details.

4.2.3 Secondary Endpoints – KCCQ-TSS change from baseline at 24 and 48 weeks

4.2.3.1 Definition

KCCQ-TSS change from baseline at 24 and 48 weeks respectively are secondary endpoints.

4.2.3.2 Derivations

The absolute change from baseline at 24 and 48 weeks respectively will be derived. See Section 4.2.1.2 for derivation of KCCQ-TSS.

4.2.3.3 Handling of Dropouts and Missing Data

See Section 4.2.1.3 describing handling of missing data for the ANCOVA estimator for details.

4.2.3.4 Primary Analysis of Secondary Endpoint

See part of Section 4.2.1.4 for details on the statistical inference. In addition, distribution of KCCQ-TSS at baseline, 12, 16, 24 and 48 weeks respectively will be presented as summary statistics.

The same hypothesis as in section 4.2.1.4 will be tested. See Section 3.3.4 for details on the hierarchical testing sequence.

4.2.4 Secondary Endpoint – 6MWD change from baseline at 24 and 48 weeks

4.2.4.1 Definition

6MWD change from baseline at 24 and 48 weeks respectively are secondary endpoints.

4.2.4.2 Derivations

The absolute change from baseline at 24 and 48 weeks respectively will be derived.

4.2.4.3 Handling of Dropouts and Missing Data

See part of Section 4.2.1.3 describing handling of missing data for the ANCOVA estimator for details.

4.2.4.4 Primary Analysis of Secondary Endpoint

See part of Section 4.2.1.4 for details on the statistical inference. In addition, summary statistics will be shown, as described in Section 4.2.2.4.

The same hypothesis as in section 4.2.1.4 will be tested. See Section 3.3.4 for details on the hierarchical testing sequence.

4.2.5 Secondary Endpoints – Change from baseline in log-transformed NT-proBNP at 16, 24 and 48 weeks

4.2.5.1 Definition

Change from baseline in log-transformed NT-proBNP at 16, 24 and 48 weeks respectively are secondary endpoints.

4.2.5.2 Derivations

The change from baseline in log-transformed NT-proBNP at 16, 24 and 48 weeks respectively will be derived.

4.2.5.3 Handling of Dropouts and Missing Data

See part of Section 4.2.1.3 describing handling of missing data for the ANCOVA estimator for details.

4.2.5.4 Primary Analysis of Secondary Endpoint

The analysis is evaluated under the primary estimand defined in Section 4.2, using ANCOVA as estimator, comparing AZD4831 Total versus placebo.

The change from baseline in log-transformed NT-proBNP is the response variable in the ANCOVA model with the same covariate model specification as in Section 4.2.1.4, but with a log-transformed baseline value. The endpoint will be analysed on a natural logarithmic scale and then back transformed to the original scale resulting in geometric means.

The change from baseline in log-transformed NT-proBNP is tested in the hypothesis testing procedure. See Section 3.3.4 for details on the hierarchical testing sequence.

Geometric mean estimates for each treatment group, geometric mean ratios between treatment groups, 95% CIs and p-value will be presented. In addition, distribution of NT-proBNP at baseline, 16, 24 and 48 weeks respectively will be presented as summary statistics including geometric mean, geometric CV, and geometric mean ratio.

4.2.5.5 Supplementary Analyses of the Secondary Endpoint

The supplementary analysis for this endpoint will be evaluated under the third supplementary estimand defined in Section 4.2 using ANCOVA. See Section 4.2.5.4 for details.

4.2.5.6 Subgroup Analysis

A subgroup analysis will be performed for the 16 weeks analysis timepoint. See Section 4.2.1.7 for details. The following variables listed for primary endpoints will not be included: Alcohol consumption, Nicotine consumption, S-Cystatin-C and Ceruloplasmin.

4.2.6 Secondary Endpoints – Echocardiographic parameters change from baseline at 16 and 24 weeks

4.2.6.1 Definition

LV-GLS, LAVI and LVMI change from baseline at 16 and 24 weeks respectively are secondary endpoints.

4.2.6.2 Derivations

The absolute change from baseline at 16 and 24 weeks respectively will be derived.

4.2.6.3 Handling of Dropouts and Missing Data

See part of Section 4.2.1.3 describing handling of missing data for the ANCOVA estimator for details.

4.2.6.4 Primary Analysis of Secondary Endpoint

See part of Section 4.2.1.4 for details on the statistical inference. The same hypothesis as in section 4.2.1.4 will be tested. See Section 3.3.4 for details on the hierarchical testing sequence. In addition, summary statistics will be shown, as described in Section 4.2.3.4.

4.2.6.5 Supplementary Analyses of the Secondary Endpoint

Supplementary analyses of LV-GLS, LAVI and LVMI change from baseline at 16 weeks will be evaluated under the third supplementary estimand defined in Section 4.2 using ANCOVA. See Section 4.2.1.6 for details.

4.2.6.6 Subgroup Analysis

Subgroup analyses will be performed for the 16 weeks analysis timepoint. See Section 4.2.1.7 for details. The following variables listed for primary endpoints will not be included: Alcohol consumption, Nicotine consumption, S-Cystatin-C and Ceruloplasmin.

4.2.7 Secondary Endpoint – Plasma Concentrations of AZD4831 by timepoint

4.2.7.1 Definition

The endpoint is plasma concentration.

4.2.7.2 Derivations

Plasma concentrations of AZD4831 by assessment timepoint will be derived. The number of observations below LLoQ will be presented and will be imputed to LLoQ/2 in the analyses.

4.2.7.3 Handling of Dropouts and Missing Data

Any missing data will not be imputed.

4.2.7.4 Primary Analysis of Secondary Endpoint

Plasma AZD4831 concentrations will be summarised by descriptive statistics for the full analysis set, by assessment timepoints and dose level.

4.2.8 Secondary Endpoint – Change from baseline in log-transformed inflammatory biomarkers at 16, 24 and 48 weeks

4.2.8.1 Definition

Change from baseline in log-transformed hsCRP and IL-6 at 16, 24 and 48 weeks respectively are secondary endpoints.

4.2.8.2 Derivations

Change from baseline in log-transformed hsCRP and IL-6 at 16, 24 and 48 weeks respectively will be derived.

If an IL-6 observation is reported with highly sensitive (hs) IL-6 lab code, this data will be included in analysis. Otherwise, the non-hs IL-6 lab code will be used.

Observations reported as LLoQ will be imputed as described in Section 3.3.1.3.

The dichotomous response variable for the logistics regression for IL-6 at 16, 24 and 48 weeks respectively is categorised as

- <3.16
- ≥ 3.16

where 3.16 is the LLoQ reported for the non-hs analysis method first used.

4.2.8.3 Handling of Dropouts and Missing Data

See part of Section 4.2.1.3 describing handling of missing data for the ANCOVA estimator for details.

4.2.8.4 Primary Analysis of Secondary Endpoint

See Section 4.2.5.4 for details on the statistical inference, hypothesis testing and presentation.

4.2.8.5 Supplementary Analyses of the Secondary Endpoint

A supplementary analysis for change from baseline in log-transformed IL-6 at 16 weeks will be evaluated under the third supplementary estimand defined in Section 4.2 using ANCOVA. See Section 4.2.5.4 for details.

In addition, the following two exploratory analyses will be performed to investigate impact of LLoQ frequency on IL-6 analyses:

- A logistic regression model with the dichotomous response variable derived in Section 4.2.8.2 and treatment group, neutrophil count stratum and baseline IL-6 value as covariates will be used to compare the active treatment groups with placebo. The observed number and proportion of subjects in the below or equal to and over LLoQ for IL-6 respectively, and odds ratios comparing active treatment groups against placebo along with 2-sided 95% confidence intervals and p-value will be presented.

- An analysis using ANCOVA as specified in using only subjects with either hsIL-6 data (using hs lab test or reflex test for high values) at both baseline or 16 weeks, or IL-6 (using standard lab test) at both baseline or 16 weeks will be performed with model specification and presentation as described in Section 4.2.5.4, with the addition of a binary lab test covariate to the model.

4.2.8.6 Subgroup Analysis

Subgroup analyses will be performed for the 16 weeks analysis timepoint. See Section 4.2.1.7 for details. The following variables listed for primary endpoints will not be included: Alcohol consumption, Nicotine consumption, S-Cystatin-C and Ceruloplasmin

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4.2.16 Exploratory Endpoint – Time to cardiovascular event

4.2.16.1 Definition

Estimands

The following attributes define the estimand used to evaluate the primary analysis of this endpoint.

- **Endpoint:** Time to the first occurrence of any event in the composite event variable consisting of HF hospitalisation, urgent HF visits with requirement for additional loop diuretic treatment, MI, cardiovascular deaths, and all-cause mortality.

- **Treatment:** Randomised treatment group (regardless of actual received treatment), AZD4831 2.5mg/5mg or placebo.

- **Population:** Subjects aged ≥ 40 years with an established diagnosis of HF with LVEF > 40%, and at least one or more of structural heart disease, signs of increased left ventricular filling pressure, signs of significant diastolic dysfunction, or a recent hospitalisation for decompensated HF. Implemented by FAS.

- **Population-level summary:** Kaplan-Meier (KM) estimate by treatment group, difference in KM estimate between treatment groups and hazard ratio (HR) between treatment groups.

- **Handling of intercurrent events:** Treatment policy strategy combined with composite variable strategy.

    - Initiation or change of concomitant medication and permanent premature discontinuations will be handled by a treatment policy strategy, i.e., ignoring these intercurrent events, implemented by including all available data.

4.2.16.2 Derivations

Time (in days) from randomisation to first event in composite variable will be derived. In addition, time (in days) from randomisation to first event for each individual component is derived.

The Planned treatment period will be used. See Section 3.3.1.8 for censoring rule.

Deaths reported as 'cause undetermined' will be included as non-CV deaths in the analysis.

4.2.16.3 Handling of Dropouts and Missing Data

Any missing data will not be imputed. See Section 3.3.1.8 for details on time-at-risk and censoring.

4.2.16.4 Primary Analysis of Exploratory Endpoint

The risk for an event at 48 weeks will be evaluated under the estimand defined in Section 4.2.16.1 and estimated using KM % estimates. AZD4831 Total and placebo will be compared using a Cox regression model with factors for treatment group and stratified by neutrophil count. The Efron method for ties and p-value based on the score statistic will be used.

The composite event and individual components will be analysed separately using the same model and the contribution of each component of the primary composite endpoint to the overall treatment effect will be presented. For the individual component analyses, all first events of the given type will be included irrespective of any preceding non-fatal composite event of a different type.

For the interim analysis/es, the risk for an event at 16 weeks will be estimated.

Presentation

The number of events, Kaplan-Meier %, HR with 95% CI and p-value will be presented. KM% estimates of the cumulative distribution function of subjects with the composite event as well as the individual component will be plotted comparing all treatment groups.

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4.3 Pharmacodynamic Endpoint(s)

Inflammatory biomarkers will be analysed as described in Sections 4.2.8 and 4.2.14.

4.4 Pharmacokinetics

Plasma concentrations of AZD4831 will be presented as described in Section 4.2.7.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and electrocardiogram (ECG).

Tables, figures, and listings are provided for SAS unless otherwise stated. All tabulations of safety data (AEs, laboratory parameters, vital signs, and ECG) will be based on both the On-treatment period and On-study period respectively unless otherwise stated.

The analyses will be presented for AZD4831 2.5mg, AZD4831 5mg, AZD4831 Total (pooled treatment groups AZD4831 2.5mg and 5mg) and placebo, unless otherwise stated.

Safety estimand definition

The aim with the analyses of safety data is to assess the general safety objective; this will be done for a hypothetical scenario where study treatment is not prematurely discontinued. Two different handling of intercurrent event strategies are considered complementary to assess this hypothetical scenario for all safety endpoints:

- On-treatment; unbiased under the assumption that censoring following premature treatment discontinuation is non-informative. Note that this approach could also be described as handling premature treatment discontinuation with a hypothetical strategy.
- On-study; unbiased under the assumption that the risk for an event is independent of continued treatment. Note that this approach could also be described as handling premature treatment discontinuation with a treatment policy strategy.

Hence, the general safety objective will be assessed through two complementary estimands with respect to handling of the intercurrent event of premature discontinuation of study treatment, defined by the following attributes:

- **Population**: Subjects with an established diagnosis of HF with LVEF > 40%, as defined by the inclusion and exclusion criteria, who have received at least one dose of IP. Implemented using the safety analysis set.
- **Treatment**: Actual treatment group (i.e., not necessarily the treatment a subject was randomised to), AZD4831 2.5mg/5mg or placebo.
- **Intercurrent events**:
    - Premature study treatment discontinuation: All analyses will be provided using two complementary strategies:
        - Hypothetical strategy: Premature study treatment discontinuation cannot occur, implemented by censoring data after premature study treatment discontinuation + 14 days, using the On-treatment analysis period (Section 3.3.1.5).
        - Treatment policy strategy: Ignoring study treatment discontinuation, implemented by including all available data, using the On-study analysis period (Section 3.3.1.5).
    - Initiation or change of concomitant medication, including rescue medication: Will be ignored, i.e., handled using a treatment policy strategy.
    - Death: Except for assessment of mortality, will be handled by a hypothetical strategy as it cannot occur, implemented by censoring time to event data at time of death and not imputing any data after death.
- **Population level summaries**: Distribution of endpoints by treatment group for all safety variables. Kaplan-Meier (KM) estimate for event by treatment group, difference in KM estimate between treatment groups and hazard ratio (HR) between treatment groups for AEs.

Table 4. Overview of safety objectives, endpoints and estimands for Part A

Statistical category	Endpoint	Population	Handling of inter-current events	Population level summary (analysis)	Details in section
Objective 1: To assess the safety and tolerability of AZD4831 as compared with placebo in patients with HF					
Safety	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG.	SAS	Hypothetical strategy; Treatment policy strategy	Distribution of endpoints by treatment group for all safety variables. KM estimate for event	4.6

Statistical category	Endpoint	Population	Handling of inter-current events	Population level summary (analysis)	Details in section
	Assessments related to AEs will cover: • Occurrence/Frequency • Seriousness • Death • AEs leading to discontinuation of IMP • AEoSIs related to skin reactions, including maculopapular rash, and infection Vital signs parameters include blood pressure, pulse rate, and body temperature; assessments will cover: • Observed value • Absolute change from baseline values over time • Orthostatic blood pressure A complete list of laboratory parameters is presented in Section 8.2.4 of the CSP; assessments will cover: • Observed value • Absolute change from baseline values over time • Treatment-emergent changes in selected laboratory parameters Electrocardiogram measurements assessments will cover: • Investigator evaluation			by treatment group, difference in KM estimate between treatment groups and HR between treatment groups for AEs.	

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Duration of exposure (days) to study drug will be calculated for each subject as

$$Duration\ of\ exposure\ (days) = date\ of\ last\ dose - date\ of\ first\ dose + 1.$$

Dose interruptions will not be taken into consideration for calculation of duration of exposure.

Total time of exposure (subjects-years) is calculated as

$$Total\ time\ of\ exposure = sum(duration\ of\ exposure\ for\ each\ subject)\ \div 365.25$$

4.6.1.2 Presentation

Duration of exposure and Total time of exposure will be presented descriptively by treatment group and in total.

Total exposure will be presented categorically by cumulative categories by every 28th day from Day 1 to Day 337. These categories are cumulative, and subjects will be included in all categories that apply to them.

A figure of exposure over time will be presented, with one line for each treatment group, and percentage of subjects still exposed on the y-axis and time from first dose on the x-axis. At a given time t, the curve will show the percentage of subjects with exposure time >t.

In addition, KM% estimates of the cumulative distribution function of subjects who have discontinued IP will be plotted comparing all treatment groups, applied on the planned treatment period.

Listings

Subjects who receive IP which is not consistent with the treatment he or she was randomised to receive will be listed.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse event will be assigned to the analysis period based on the onset date, as defined in Section 3.3.1.5.

Adverse events will be classified by SOC and PT and coded using Medical Dictionary for Regulatory Activities (MedDRA).

Risk for an event will be estimated using KM% estimates. Comparisons of risk for an event between the treatment groups will be estimated by HRs with 95% CIs based on a Cox regression model with a factor for treatment group, and difference in KM%. A subjects first event that occurs during the On-treatment or On-study period, respectively, will be included in the analysis. All subjects who are event free for the given AE (or AE category) will be censored according to the definitions in Sections 3.3.1.5 and 3.3.1.8.

Any AE
Defined as an AE reported with an onset date within the defined period.

Any SAE
Defined as an AE reported as serious, irrespective of outcome.

SAEs with outcome death
Defined as an AE with reported outcome as 'Fatal', there may be more than one AE with outcome death for a subject. The onset date of the AE determines the analysis period, irrespective of date of death.

AEs leading to discontinuation of IP
Defined as an AE with action taken IP reported as drug permanently discontinued. The onset date of the AE determines the analysis period, irrespective of date of discontinuation of IP.

AEs possibly related to IP
Defined as an AE that is reported as "reasonable possibility AE caused by IP". If this evaluation is missing, it will be counted as an AE possibly related to IP.

AEs by maximum intensity
AEs will be classified by the reported maximum intensity, "Mild", "Moderate" and "Severe". If this maximum intensity evaluation is missing, it will be counted as "Severe".

Adverse events of special interest
The following two groups of adverse events are Adverse events of special interest (AEoSI):

- Infections: will be identified by the SOC "Infections and infestations".
    - The pathogen specific High level group term (HLGT) "Fungal infectious disorders".
- Skin reactions, including maculopapular rash:
    - Skin reactions/rashes considered maculopapular (described as macules/papules under the morphology/appearance question).
    - Skin reactions/rashes not considered maculopapular (not described as macules/papules under the morphology/appearance question).

4.6.2.2 Presentation

For all AE tables, unless otherwise stated, the number and percentage of subjects experiencing an event along with Kaplan-Meier percentages at 16 and 48 weeks will be presented for all treatment groups. In addition, KM% differences and HR together with 95% confidence intervals will be presented for the comparisons of each active treatment group to placebo. Percentages will be calculated with number of subjects in SAS as denominator, and subjects will only be counted once per category, regardless of the number of AEs satisfying each condition.

Tables where AEs are presented by SOC and PT will be sorted by international order for SOC and alphabetical order for PT.

In addition,* KM% estimates of the cumulative *distribution function* of subjects with AEoSIs will be plotted comparing all treatment groups. *Overall summary of AEs

The following categories will be presented in the overall summary:

- any AE,
- any SAE,
- any SAE with outcome death,
- any AE leading to discontinuation of IP, and
- any AE possibly related to IP (as assessed by investigator).

Any AE leading to discontinuation of IP category will only be analysed for the On-treatment period.

By SOC and PT

Separate AE tables by SOC and PT will be presented for the following categories:

- any AE,
- AEs possibly related to IP,
- AEs leading to discontinuation of IP,
- AEs by cumulative maximum intensity (any, moderate or severe, severe),
- any SAE,
- SAE with outcome death, and

- AEs of special interest.

Most common AEs
A table of the number and percentage, and KM% at 16 and 48 weeks of the most common adverse events by PT (frequency of > 5%). This table will be sorted by decreasing frequency in AZD4831 5mg arm.

Most common non-serious AEs
A table of non-serious AEs occurring in more than 5% of subjects in any treatment group will be presented, by SOC and PT.

AEs of special interest
A mapping of the AEoSIs to Preferred terms will be presented.

For each of the SOC Infections and infestations and the HLGT Fungal infectious disorders, an overall summary, and any AE and SAE by PT will be presented. In the overall summaries, AEs by cumulative maximum intensity (any, moderate or severe, severe) will be presented in addition to categories described under Overall summary of AEs.

Skin reactions will be presented by a summary of the following categories of skin reactions:

- any skin reaction/rash
- any maculopapular skin reaction/rash leading to permanent premature IP discontinuation by cumulative maximum CTCAE grade (any, 2 or 3, 3), and
- any non-maculopapular skin reaction/rash leading to permanent premature IP discontinuation (SAEs and generalised skin reaction/rash)

For maculopapular skin reaction/rash an overall summary, maculopapular AEs by PT and maculopapular SAEs by PT will be presented. In the overall summary, AEs by cumulative maximum intensity (any, moderate or severe, severe) and AEs by cumulative maximum CTCAE grade (any, 2 or 3, 3) will be presented in addition to categories described under Overall summary of AEs.

In addition, maculopapular AEs and SAEs will be presented by cumulative maximum CTCAE grade (any, 2 or 3, 31, 2, 3), on PT level.

For other skin reactions/rashes (excluding maculopapular skin reactions/rashes) an overall summary, AEs by PT and SAEs by PT will be presented. In the overall summaries, AEs by

cumulative maximum intensity (any, moderate or severe, severe) will be presented in addition to categories described under Overall summary of AEs.

Key subject information
Key subject information will be presented for subjects with

- SAEs with outcome death,
- any SAEs, and
- AEs leading to discontinuation of IP for the full study period.

Listings
Adverse events listings will be presented for

- each individual AE,
- subjects with AEoSIs related to skin reactions (including maculopapular rash), and
- AEs reported for subjects who received the incorrect IP, i.e., not the randomised IP.

Narratives
Narratives will be generated for all deaths, AEs leading to discontinuation of IP, AEs of special interest and SAEs.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry and haematology will be collected according to the schedule of activities in Section 1.3 of the CSP. Clinical Safety Laboratory Assessments are listed in Section 8.2.4 of the CSP.

Treatment emergent abnormalities
Treatment emergent abnormalities in selected parameters for haematology and chemistry laboratory measurements are defined as post-baseline measurements meeting the pre-defined criteria for abnormality below and is more extreme than the non-missing baseline value for a subject. Thus, if the baseline value met the criteria for marked abnormality and the post-baseline value is equal to or less extreme than the baseline value, this is not considered a treatment emergent abnormality. Low and high ranges are derived based on reference ranges provided by the central laboratory, if available.

- Haematology:

- Eosinophils ≥ 0.7 x 10^9/L; ≥1.5 x10^9/L
- Haemoglobin < 100 g/L; < 80 g/L
- Neutrophils < 1.5 x 10^9/L; < 1.0 x 10^9/L
- White blood cell count < 3.0 x 10^9/L; < 2.0 x 10^9/L

- Chemistry:
  - Creatinine: ≥ 1.5x baseline creatinine and ≥ 2x baseline creatine
  - ALP > 1.5 x ULN; > 3 x Upper limit normal (ULN)
  - ALT > 3 x ULN; > 5 x ULN; > 10 x ULN
  - AST > 3 x ULN; > 5 x ULN; > 10 x ULN
  - TB > 1.5 x ULN; > 2 x ULN
  - AST or ALT > 3 x ULN
  - AST or ALT > 3 x ULN and TB > 2x ULN
  - TSH > 6 mIU/L; ≥10 mIU/L
  - TSH > 6mIU/L and free T4 < Lower limit normal (LLN); ≥10mIU/L and free T4 < LLN

For criteria comprising combinations of parameters, the treatment emergent abnormality is flagged when both parameters meet their individual criteria on same visit.

4.6.3.2 Presentations

Clinical laboratory parameters will be presented for SAS by treatment group, and scheduled visit, separately for haematology and chemistry parameters, and the parameters will be presented in alphabetical order.

Values and absolute change from baseline will be presented for continuous variables using descriptive statistics for all scheduled assessments after baseline.

Maximum on-treatment/on-study ALT and AST versus maximum on-treatment/on-study total bilirubin will be presented, by treatment group

Treatment emergent abnormalities

The number of subjects with observations meeting the pre-specified abnormality laboratory criteria in Section 4.6.3.1 for each parameter will be presented, for SAS.

Key subject information

Key subject information will be presented for subjects with treatment emergent abnormalities as defined and listed in Section 4.6.3.1.

Subjects meeting potential Hy's laws criteria will be presented as key subject information, with treatment group presented by page.

Listings

A listing of individual laboratory measurements, including reference range indicator will be presented.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Clinical laboratory parameters for urinalysis collected according to the schedule of activities according to Section 1.3 of the CSP. Clinical Safety Laboratory Assessments are listed in Section 8.2.4 of the CSP.

Treatment emergent abnormalities

Subjects with treatment emergent urinalysis parameter abnormalities in quantitative parameters will be defined according to the non-mutually exclusive thresholds based on central laboratory ranges (when applicable): <LLN, >ULN.

4.6.4.2 Presentations

Clinical laboratory parameters for urinalysis will be presented for SAS by treatment group, and the parameters will be presented in alphabetical order.

Change from baseline to maximum and minimum assessment on-treatment and on-study respectively will be presented in shift tables.

Treatment emergent abnormalities

The number of subjects with observations meeting the pre-specified abnormality laboratory criteria in Section 4.6.4.1, for each parameter will be presented, for SAS.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Treatment emergent abnormalities

Treatment emergent ANCA positivity is defined as shifts from negative at baseline to positive post-treatment.

'Negative' results will be mapped to negative category. Results not reported as 'Negative' will be mapped to positive category.

4.6.5.2 Presentations

Treatment emergent abnormalities

The number of subjects with treatment emergent ANCA positivity will be presented in a shift table with the categories positive and negative, by treatment group.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs (supine blood pressure (BP), pulse rate and body temperature) will be performed at timepoints according to the schedule of activities in Section 1.3 of the CSP.

For baseline vital signs assessments, the following order of eCRF forms should be used.

- VS4 (if not missing),
- VS3 (if VS4 is missing),
- VS5 (if both VS4 and VS3 are missing),

If all above are missing, earlier assessments should be used.

Observations from VS7 will not be considered as baseline since this is completed post first dose of IP as per the eCRF instructions.

The same logic applies to all post-randomisation visits.

Vital signs shift from baseline will be defined based on the following categorisation:

- Systolic BP: High if ≥140; Normal if <140 and ≥90; Low if <90
- Diastolic BP: High if ≥90; Normal if <90 and ≥60; Low if <60
- Pulse rate: High if ≥100; Normal if <100 and ≥50; Low if <50.

Treatment emergent abnormalities

Vital sign treatment emergent abnormalities are determined as follows:

- Systolic BP (mmHg):
  - Observed value ≥ 140 and absolute increase of ≥ 20 from baseline for high level.
  - Observed value < 90 and absolute decrease of ≥ 20 from baseline for low level.
- Diastolic BP (mmHg):
  - Observed value ≥ 90 and absolute increase of ≥ 10 from baseline for high level.
  - Observed value < 60 and absolute decrease of ≥ 10 from baseline for low level.
- Pulse rate (beats/min):
  - Observed value ≥ 100 and absolute increase of ≥ 20 from baseline for high level.
  - Observed value < 50 and absolute decrease of ≥ 20 from baseline for low level.

4.6.6.2 Presentations

Values and absolute change from baseline will be presented based on SAS by visit for continuous variables using descriptive statistics for all scheduled assessments after baseline, by treatment group.

Vital sign shift from baseline to maximum/minimum on-treatment/on-study value will be presented.

Treatment emergent abnormalities

The number and percentage of subjects with vital signs treatment emergent abnormalities will be presented by treatment group.

Key subject information

Key subject information will be presented for subjects with treatment emergent abnormalities as defined in Section 4.6.6.1.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Single 12-lead ECG (standard ECG with a paper speed of 25-50 mm/second covering at least 6 sequential beats) will be obtained according to the schedule of activities in Section 1.3 of the CSP.

Treatment emergent abnormalities

ECG treatment emergent abnormalities are defined as subjects with abnormal clinically significant results that were not present at baseline.

4.6.7.2 Presentations

Summary statistics will be shown for the following categories for SAS by treatment group:

- Heart rhythm category
- Overall ECG evaluation
- Was the ECG clinically significant?

Shifts from baseline to last observation in ECG overall evaluation will be analysed in terms of normality and clinical significance.

Treatment emergent abnormalities

The number and percentage of subjects with ECG treatment emergent abnormalities will be presented by treatment group for SAS, where the percentage is based on number of subjects per treatment group with a baseline value and at least one post-baseline value.

Key subject information

Key subject information will be presented for subjects with treatment emergent abnormalities.

Listings

A listing for all subjects will present date of ECG performance, categories listed above and reasons if conduction was abnormal.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Orthostatic blood pressure test

Orthostatic hypotension related measures are derived from the orthostatic BP measurements. The orthostatic hypotension test is described in section 8.2.2 in the CSP. It was communicated to sites on 12 August 2022 to stop performing the post-dose assessment at the day of randomisation.

Therefore, only subjects randomised prior to 12 August 2022 will be at risk in the analysis presenting results for the post-dose test at the day of randomisation. All observations will be presented in the listing regardless of when the test was performed.

The following definitions will be applied:

- BP decrease: a decrease ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure.
- BP decrease reported as AE: a BP decrease and a reported AE of Orthostatic Hypotension the same day post-first dose or within the same day of the 12 weeks measurement.
- Symptomatic BP decrease: BP decrease which the investigator judge that there were symptoms that were related to the orthostatic blood pressure measurement.
- Asymptomatic BP decrease: BP decrease which the investigator judge that there were no symptoms that were related to the orthostatic blood pressure measurement.

These categories will be presented at three timepoints

- post-first dose irrespective of baseline status,
- only post-first dose (including only subjects with no observed BP decrease pre-first dose), and
- at 12 weeks.

4.6.8.2 Presentations

Orthostatic blood pressure test

Measurements related to the Orthostatic hypotension test will be summarised for each of the three timepoints described in Section 4.6.8.1 by number and percentage of subjects with an event and total number of events based on the safety analysis set, by treatment group.

Listings

A listing of all subjects with at least one test sequence suggestive of Orthostatic hypotension will be presented.

A listing of AEs, SAEs and DAEs by SOC/PT for subjects with at least one test sequence suggestive of Orthostatic hypotension will be presented. Adverse events occurring within 3 hours after first dose of IP for the baseline visit or the 12 weeks measurement will be flagged.

5 INTERIM ANALYSIS

At least one, but possibly several, interim Analyses for Part A with the purpose of informing further development of the clinical programme will be conducted, including but not limited to dose selection for Part B. The first interim analysis will be performed when at least 150 randomised subjects have had the possibility to reach the 16 weeks visit. The last interim analysis will be performed when all participants in Part A have completed the last protocol-specified visit/assessment (the last Week 52 visit [including telephone contact]). An Unblinded Review Committee (URC) will review each of the interim analyses. If Part B were not to start or progress, then the last interim would not be regarded as an interim but would become the final analysis.

Further details of the interim analysis, e.g., members of the URC, scope of analysis, Go/No go criteria for further clinical development and descriptions of unblinding procedures and meetings, are presented in a separate URC Charter.

6 REFERENCES

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