A Phase IIb Randomised, Double-blind, Placebo-controlled, Multi-centre, Dose-ranging Study of AZD3427 in Participants with Heart Failure and Pulmonary Hypertension due to Left Heart Disease (WHO Group 2)

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
6MWD	6-minute walk distance
ACE/ARB	Angiotensin-Converting Enzyme/ Angiotensin Receptor Blockers
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase/transaminase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
BLQ	Below lower limit of quantitation
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CK	Creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CSP	Clinical study protocol
CV	Cardiovascular
DAE	Discontinuation due to AE
DBP	Diastolic blood pressure
DCO	Data cut-off
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiogram
EDV	End diastolic volume
E/E’	Early mitral filling velocity/early diastolic mitral annular velocity (ratio)
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ERR	Extended reference range
ES	Enrolled analysis set
ET	Early termination
FAS	Full analysis set
FCS	Fully conditional specification
FDAAA	Food and Drug Administration Amendments Act
FC	Functional Class
HF	Heart failure
HR	Heart rate

hsCRP	High-sensitive C-reactive protein
hs-TnT	High-sensitive troponin T
IA	Interim analysis
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	Investigational product
IMP	Investigational medicinal product
IPD	Important protocol deviation
ISR	Injection site reaction
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Symptom Score
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire – Overall Symptom Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire – Total Symptom Score
KIM-1	Kidney injury molecule1
LAVi	Left atrial volume index
LARS	Left atrial reservoir strain
LH	Luteinising hormone
LLOQ	Lower limit of quatitation
LV	Left ventricular
LV EDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LV SVi	Left ventricular stroke volume index
LVGLS	Left ventricular global longitudinal strain
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model repeated measures
mPAP	Mean pulmonary arterial pressure
MRA	Mineralocorticoid receptor antagonist
mrEF	Midrange ejection fraction
NA	Not applicable
NAbs	Neutralising antibodies
NC	Not calculated
NQ	Not quatified
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
NYHA FC	New York Heart Association functional class
PAP	Pulmonary arterial pressure
PARM	Planned analysis review meeting

PASP	Pulmonary arterial systolic pressure
PAWP	Pulmonary artery wedge pressure
PH	Pulmonary hypertension
PIIINP	Procollagen 3 N-Terminal Propeptide
PD	Pharmacodynamic(s)
pEF	Preserved ejection fraction
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PRO-C6	P204 endotrophin
PT	Preferred Term
PVR	Pulmonary vascular resistance
Q1	First quartile
Q3	Third quartile
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
rEF	Reduced ejection fraction
RHC	Right heart catheterisation
RV/LV	Right ventricle/left ventricle
RV EDA	Right ventricular end-diastolic area
RV FAC	Right ventricular fractional area change
RVOT AT	Right ventricular outflow tract acceleration time
RXFP1	Relaxin/insulin-like family peptide receptor-1
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
SMQ	Standardised MedDRA Queries
SoA	Schedule of activities
SOC	System Organ Class
SS	Safety analysis set
SV	Stroke volume
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TE	Treatment-emergent
TELVC	Treatment-emergent laboratory/vital sign change
TGF-β	Transforming growth factor beta
TNF-α	Tumour Necrosis Factor-alpha
TRV	Tricuspid regurgitation velocity

TSS	Total symptom score
uACR	Urine albumin-creatinine ratio
ULN	Upper limit of normal
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY Change refers to:	Date (Month/Day/Year)	Description of change	In line with CSP?	Rationale
NA	5/15/2023	Initial approved SAP	NA	NA
Statistical analysis method for Primary endpoint(s)	7/4/2023	Add analysis details for subgroup analysis in section 4.2.1.7	NA	
Statistical analysis method for secondary endpoint(s)	7/4/2023	Add analysis details for subgroup analysis in section 4.2.2.7	NA	
Statistical analysis method for secondary endpoint(s)	7/4/2023	Remove description of missing answer in section 4.2.3.3	Yes	
	7/7/2023	SAP version 2.0	NA	NA
Primary endpoint(s)	7/12/2024	1. Update descriptions of estimand (treatment policy) and add second estimand (hypothetical) 2. Add the details of missing data handling (multiple imputation under MAR assumption and wash-out approach, 3. Add AppendixA.2 for imputation details	Yes	Aligned the SAP to CSP

Statistical analysis method for primary endpoint(s)	7/12/2024	1. Add analysis details for subgroup analysis. 2. Update the modelling for comparisons between high pooled and total pooled versus placebo 3. Added a new 4.2.1.5 Secondary Analyses of Primary Endpoint (secondary estimand) 4. Add clinical questions in section 4.2.1.1 and 4.2.1.5 for both estimands	Yes	Aligned the SAP to CSP
Secondary endpoint(s)	7/12/2024	1. Update descriptions of estimand and add second estimand	Yes	CSP amendment v3 and align SAP to CSP
Statistical analysis method for secondary endpoint(s)	7/12/2024	1. Add the details of the analysis using the primary estimand, i.e. missing data handling (multiple imputation under MAR assumption and wash-out approach, details added in AppendixA.2) 2. Update the modelling for comparisons between high pooled and total pooled versus placebo. 3. Remove sensitivity analyses and supplementary analyses on 6MWD, KCCQ-TSS, NYHA FC. 4. Clarify the category of NYHA FC in the analysis model and add a shift tables for change from baseline in NYHA FC.	Yes	1-2. Align SAP to CSP 3. Simplification 4. Clarification

Data presentation	7/12/2024	1. Pharmacokinetics section: a. Add descriptions for scatter plot of dose normalized individual geometric mean concentration of AZD3427 versus baseline body weight (kg)/ baseline eGFR (mL/min/1.73m²). b. Update the content to the latest internal guidance. 2. Immunogenicity section: Update the content to the latest internal guidance. 3. Safety section: a. Replace on-treatment period with on-study treatment for safety analyses. b. Adverse events i. Add tables for AE by ADA category, possibly related SAE, AE leading to withdrawn from study. ii. Update the descriptions of title of Key participants information for participants with hypersensitivity reactions assessed by Principal Investigator and by-participant listing of all AEs including SAEs occurred prior to date of randomisation. c. Clinical laboratory i. Add figures for haemoglobin and haematocrit over time and change from baseline.	Yes	1.-2. Update to align with latest AZ guidance. 3. CCI [redacted] Other update: include additional safety data presentation and clarification.

		d. Vital sign i. Add outputs for SBP/DBP/HR over time for participants with AEs of hypotension. ii. Add figures for change in mean/ mean (+/- SD) vital sign parameters at Week 1 and Week 3 over time. iii. Add a row for treatment emergent abnormality of body weight in section 4.5.6.		

Other	7/12/2024	1. Exploratory endpoint a. Plasma, serum, and urine biomarkers section: indicate OLINK data will not be included in CSR. b. Modify the content in 4.2.7.1 primary analysis of capability of echocardiographic parameters to diagnose of PH Group 2. c. Derivations of the Time to cardiovascular (CV) death, HF hospitalisation, or outpatient visit due to HF deterioration in section 4.2.8.1 d. Include the details to the title of 4.2.9 Clinical benefit at Week 25, consisting of a composite of all-cause death, HF hospitalisations, outpatient visit due to HF deterioration and change from baseline at Week 25 in KCCQ-TSS/6MWD. e. Add KCCQ-CSS/OSS as exploratory endpoints and analysis by ANCOVA f. Add appendix C to the calculation of KCCQ-CSS/OSS 2. Modify abbreviation list. 3. Remove duplicate information from SAP and refer to CSP (SoA and tables of lab assessments). 4. Modify the descriptions based on team comments in following section which do not change the content:	Yes	1. Clarification of the intention of the exploratory analysis. Update and align SAP to CSP amendment v3 2. Editorial change 3. Simplification 4. Clarification and align SAP to CSP

		1. introduction, 2. changes to protocol planned analyses, 3.2 PK analysis populations, 3.3.1.3 definition of baseline values, 3.3.3 handling of unscheduled visits, 3.3.4 missing data, 4.1.1.2 presentation of study population, derivation for 4.1.5 baseline characteristics, derivation for 4.1.6 disease characteristics, derivation for 4.1.8 prior and concomitant medication, Presentation for 4.1.9 Study drug compliance, 4.2 endpoint analyses (layout of Table 2), 4.2.5.2 derivation of eGFR, 4.2.5.4 primary analysis of secondary endpoint (add wording of FAS), 4.5 safety analyses section, 5. interim analysis, 6. analysis of data from China and Asia.		
	7/12/2024	SAP version 3.0	NA	NA
Data presentation	11/29/2024	1. Remove geometric mean percentage change in section 4.2.1.4. 2. Add a category for the urinalysis shift table in section 4.5.4.2. 3. Update the definition of on-study period in section 4.5.2.1.	Yes	1. Geometric mean percentage change is not required since the comparison between AZD3427 versus placebo will be based on the geometric mean ratio after the back-transformation 2. Correction of categories 3. Add to enhance clarity
Derivation of primary endpoint(s)	11/29/2024	1. Update the definition of subjects included in supplementary analysis in section 4.2.1.8	Yes	1. Update to enhance clarity

Derivation of secondary endpoint(s)	11/29/2024	1. Add the definition of subjects included in supplementary analysis in section 4.2.2.8	Yes	1. Add to enhance clarity

Data presentation	9/18/2025	1. Update the description of log-transformation in section 4.2.2. 2. Update the categories of urinalysis in section 4.5.4.2. 3. Add “log-transformed” of exploratory endpoints (plasma, serum, and urine biomarker) in Table 2 4. Remove section of sensitivity analysis for the secondary endpoint of echocardiographic parameters. 5. Update the wordings in section 4.2.8. 6. Update the wording in section 4.2.1.1 and 4.2.1.5. 7. Update the wording in Appendix A.2. 8. Remove exposure days in section 4.1.1.2. 9. Update the wording in section 3.3.6. 10. Remove ADA cross reactive to relaxin in section 4.4.1. 11. Update the descriptions of Nab analysis in section 4.4.1. 12. Add a table for loop diuretics in section 4.1.8 13. Update reference of section in Table 2. 14. Add the calculation of PVR in section 4.2.1.2. 15. Update the descriptions in section 4.2.6.1. 16. Update descriptions in section 4.2.9.2.	Yes	1-10. Update to enhance clarity 11. Update based on CSP v4 12.-24. Update to enhance clarity 25.-29. Update based on dry run comments

		17. Update plasma to serum in section 4.3. 18. Add Treatment emergent urinalysis abnormalities by predefined criteria in section 4.5.4.1 and 4.5.4.2. 19. Modify the wording in section 6.2. 20. Add variables in section 4.2.2 and 4.2.3 21. Update the description of exploratory endpoint (clinical benefit) in Table 2 in Section 4.2 22. Move 21 ECHO parameters and 7 RHC parameters as exploratory endpoints to make it consistent with CSP. 23. Add orthostatic hypotension in section 4.5.6.2 24. Update analysis set of line plot in section 4.2.5.4. 25. Update the definition of loop diuretics initiated during study "treatment" period in section 4.1.7 26. Modify the categories of NYHA FC and LVEF subgroup in section 4.2.1.7 27. Add cardiac index section 4.1.6 and modify the unit in this section 28. Include descriptions of additional outputs (supplementary analysis for secondary endpoints of ECHO parameters, line plot of change in Haemoglobin, Haematocrit, Weight, box plot of urine albumin/creatinine)		

		in section 4.2.3.7, 4.5.3.2, 4.5.4.2, 4.5.6.2. 29. Include 10 secondary ECHO parameters in disease characteristics table		
Other	9/5/2025	1. Adjust list of abbreviations 2. Update version number in INTRODUCTION section 3. Correct the typo in the formula in Appendix C Calculations of confidence interval and p-value of win ratio. 4. Update Calcium, albumin corrected to Calcium in Section 4.5.3.1 5. Update spelling of hematology/hemoglobin/hematocrit	Yes	1. Update based on sponsor comments 2. Update based on CSP v4 3.-5. correction
	9/23/2025	SAP version 4.0	NA	NA

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D8330C00003 supporting the clinical study report. The reader is referred to the CSP and the eCRF for details of study conduct and data collection.

The content of this SAP is based on the following study documents:

- Study D8330C00003 protocol Version 4.0 20 November 2024.
- Electronic Case Report Form (eCRF) Version 9.0 10 December 2024.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

According to Protocol section 9.4.2.2, the estimand of Kansas City Cardiomyopathy Questionnaire (KCCQ) and Six-Minute Walking Distance (6MWD) will use a while-alive strategy, whereby death is considered an intercurrent event. As these endpoints are collected at baseline and Week 25, the while-alive strategy is not appropriate and therefore in the statistical analysis plan the study team decided to use treatment policy strategy instead, which is consistent with the primary estimand.

For the definition of safety analysis set, the participants are evaluated according to the treatment assigned at randomization.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

An interim analysis (IA) will be performed by an Independent Unblinded Review Committee after approximately 50% of participants complete Week 25 (Visit 15) with an option to trigger early initiation of Phase III activities. The IA will assess, but not be limited to pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), Six-Minute Walking Distance (6MWD), Kansas City Cardiomyopathy Questionnaire (KCCQ), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), renin, AZD3427 serum concentration, and safety.

Final database lock and the final analysis will be performed after the last participant completes the Follow-up Visit (Week 31, Visit 16) and the results of final analysis will be used to write the Clinical Study Report. Data for participants ongoing in Extended Follow-up at database lock will be reported in a CSR addendum.

3.2 Analysis Populations

For the purposes of analysis, the following populations are defined:

Population	Description

Enrolled Analysis Set (ES)	All participants who sign the ICF.
Full Analysis Set (FAS)	The Full Analysis Set consists of all participants who are randomised and have received at least one dose of study intervention. Participants are evaluated according to the treatment assigned at randomisation. The Full Analysis Set will be used for study population and efficacy analyses.
Safety Analysis Set (SS)	The Safety Analysis Set consists of all participants who have received at least one dose of study intervention. Participants are evaluated according to the treatment assigned at randomization. The Safety Analysis Set will be used for safety analyses.
PK Analysis Set (PKAS)	The PK Analysis Set consists of all participants in the Full Analysis Set who have at least one detectable AZD3427 serum concentration measurement post-treatment above lower limit of quantification. The PK Analysis Set will be used for PK analyses.
Per Protocol Set (PPS)	The Per Protocol Analysis Set consisting of all participants with no important protocol deviations identified as impact for data analysis as per the protocol deviation assessment plan and last dose and right heart catheterization within visit windows according to the protocol.

ICF = Informed Consent Form; PK = pharmacokinetic(s).

3.3 General Considerations

All study population variables will be summarised by treatment group and total. All efficacy variables will be summarized by treatment group and will also include a total pooled AZD3427 group (comprising of 1.1, 5.4, and 30.0 mg treatment groups) and a high pooled AZD3427 group (comprising of 5.4 and 30.0 mg treatment groups). All safety variables will be summarized by AZD3427 treatment group, pooled AZD3427, and placebo. Descriptive statistics (n, mean, Standard Deviation, median, minimum, and maximum for continuous data that is expected to be normally distributed; n, geometric mean, coefficient of variation, median, minimum, and maximum for continuous data that is expected to be lognormal; and n, frequencies and percentages for categorical data) will be used. Data will be summarised by time point/visit, as applicable. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to one more decimal place than the raw data recorded in the database. Percentages will be presented to 1 decimal place. If the percentage is 100%, do not present a decimal. If the percentage is 0, do not present the percentage. The p-values and confidence intervals will be presented to 3 decimal places. In general, the maximum number of decimal places reported shall be four for any summary statistics.

For analyses with treatment comparisons, comparisons will be done for each AZD3427 group versus placebo as well as the total pooled AZD3427 group (comprising of 1.1, 5.4, and 30.0 mg treatment groups) versus placebo, and the high pooled AZD3427 group (comprising of 5.4 and 30.0 mg treatment groups) versus placebo. The pooled AZD3427 groups versus placebo comparisons are included to provide results under assumptions that all, or the two highest doses, are similar with respect to efficacy and or safety. Unless

otherwise stated comparisons of pooled treatment groups using statistical modelling will be obtained using linear contrasts.

P-values will be presented as 2-sided without multiplicity adjustments. Confidence intervals will be presented as 95%.

Analyses defined as exploratory in the CSP may be reported outside of CSR. Additional exploratory or sensitivity analyses of the data may be conducted as deemed appropriate and may document in a separate analysis plan.

3.3.1 General Study Level Definitions

3.3.1.1 Study day

Relative day will be calculated following the algorithm below:

If the event occurred on or after the date of first study drug administration, then the following calculation is used:

$$Study\ Day = \ Date\ of\ event - \ Date\ of\ first\ dose + 1$$

If the event occurred before the date of first study drug administration, then the following calculation is used:

$$Study\ Day = \ Date\ of\ event - \ Date\ of\ first\ dose$$

3.3.1.2 Analysis Periods

On-study analysis period

The on-study analysis period starts on the date of first dose of study intervention and ends on the date of last clinical event assessment, unless the participant dies while under follow-up, then the date of death is taken as the end of the period. If a participant withdraws consent to continue in the study, then the on-study analysis period ends on this date at the latest.

3.3.1.3 Definition of Baseline values

In general, the baseline value for statistical analysis is the last non-missing value prior to or on the same date as the administration of the first dose of study intervention. If there are more than one assessment equally eligible to assess participant status at baseline (for example, several assessments on the date of randomisation visit and occurring either at the same time or with no time collected), the average of the non-missing values should be taken as the baseline value. For non-numeric assessment, the most normal assessment will be selected as baseline.

3.3.2 Visit Window

The Study Day for each visit is defined based on the date of first dose (Day 1). Per the protocol, visit windows of ±3 days are permissible for visits from Week 3 to Week 23; for the Week 25 visit, a window of -7/+3 is permissible; for the Follow Up Visit (Week 31), the permissible window is also ±3 days. If participation in the study is terminated early, the participant should return for an ET Visit as soon as possible. Early termination participants should still be requested to do a safety Follow-up Visit 8 weeks after their last dose.

For visit-based summary tables, variables are summarised based on the scheduled days with adjusted analysis-defined visit windows. For by-participant listings, the unadjusted visit will be used. The adjusted analysis-defined windows are summarised in Table 1:

Table 1 Visit Windows

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline/Day 1	1	Study Day <=1
Week 3	15	2<= Study Day <=21
Week 5	29	22<= Study Day <=35
Week 7	43	36<= Study Day <=49
Week 9	57	50<= Study Day <=63
Week 11	71	64<= Study Day <=77
Week 13	85	78<= Study Day <=91
Week 15	99	92<= Study Day <=105
Week 17	113	106<= Study Day <=119
Week 19	127	120<= Study Day <=133
Week 21	141	134<= Study Day <=147
Week 23	155	148<= Study Day <=161
Week 25	169	162<= Study Day <=175
Week 31	211	176<= Study Day

3.3.3 Handling of Unscheduled Visits

Data from all scheduled and unscheduled visits are included in the visit windows defined in Section 3.3.2. If there are multiple data (including scheduled, unscheduled, and ET visit) available over the same period of time, the data obtained on the date/time closest to the reference date will be utilized; the later date/time will be applied if the numbers of days/time from the reference date/time are equal in all analyses except for vital signs measurements. For vital signs measurements, the earlier date/time will be applied if the numbers of days/time from the reference date/time are equal. The only exception of above rule is the assessments scheduled for multiple timepoints (e.g. vital signs at pre-dose, 20 minutes, 40 minutes, and 60 minutes post-dose). The assessments scheduled for multiple timepoints will be included into the analysis once they fall into scheduled timepoints.

3.3.4 Missing Data

Details about imputation of partial or missing dates are given in Appendix A.1.

Intercurrent events (ICH E9R1) are events which occur after the treatment initiation and make it impossible to measure a variable of influence or how it should be interpreted. Two efficacy estimands are defined to address intercurrent events in Section 4.2. Other sporadically missing data will be using missing at random (MAR) assumption for handling missing data.

3.3.5 Multiplicity/Multiple Comparisons

No adjustments for multiple comparisons will be performed in this study.

3.3.6 Handling of Protocol Deviations in Study Analysis

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document at study start. IPDs will be reviewed as part of the ongoing data cleaning process and all IPDs will be identified and documented. IPDs will be finalised prior to database lock in a Planned Analysis Review Meeting (PARM).

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

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

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

A clear account of the disposition of all participants who enter the study will be provided. A study participant (i.e., a participant is "enrolled") is defined as someone having a signed informed consent available.

Completed treatment will be defined as a participant who completed 24 weeks of treatment period and did not discontinue treatment prematurely. The end of study is defined in the CSP Section 4.4.

Completed study will be defined as a participant who completed treatment period and completed the Follow-up Visit (Week 31, Visit 16).

4.1.1.2 Presentation

Participant disposition including screen failures will be listed and summarised for all participants enrolled, overall and by treatment group and total, where applicable. The number and percentage of participants for the following will be summarised:

- Participants screened
- Screen failures
- Participants randomised
- Participants who started treatment
- Participants who discontinued treatment
- Participants who completed treatment
- Participants ongoing on treatment at data cut-off date (interim only)
- Participants ongoing in study at data cut-off date (interim only)
- Participants completed study
- Participants withdrawn from study:
  - Discontinued treatment with a Follow-up Visit.
  - Discontinued treatment without a Follow-up Visit.
  - Completed treatment without a Follow-up Visit.

Recruitment per country and site and stratification factor will be summarized. Participants who discontinued and completed the study will be listed, including standardised disposition term, reason, description, and study day of event.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

For the definition of each analysis set, please refer to Section 3.2.

4.1.2.2 Presentation

The analysis set will be summarized for all participants enrolled by treatment group and totals. Any exclusions from analysis sets will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

For the definition of protocol deviations, please refer to Section 3.3.6.

4.1.3.2 Presentation

The incidence of IPDs will be listed and summarised for the FAS by deviation categories. The number and percentage of participants in the following categories of IPDs will be summarised:

- AE/SAE
- Disallowed medications

- Inclusion/Exclusion Criteria
- Informed Consent
- IP Administration/Study Treatment
- Procedures/Tests
- Visit Schedule
- Discontinuation Criteria
- Other

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age will be grouped accordingly in the following categories: <50, 50-64, 65-74 and >=75 years. The number of participants in each race category includes those who select that particular category.

4.1.4.2 Presentation

Demographics will be summarised and listed based on the FAS by treatment group and total. The following will be summarised: age, age group, sex, race, ethnicity, and country.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

There are no additional definitions to be defined.

4.1.5.2 Presentation

Baseline characteristics will be listed and summarised for the FAS by treatment group and totals. The following will be summarised: height, weight, and BMI.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Ejection fraction (EF) category will be defined as:

- Reduced EF (rEF): <= 40%
- Midrange EF (mrEF): > 40% to 49%
- Preserved EF (pEF): >= 50%

4.1.6.2 Presentation

Disease characteristics at baseline will be summarised and listed for all participants in the FAS by treatment group and totals.

Summaries will be produced that present:

- New York Heart Association Functional Class (NYHA FC)
- EF category (rEF, mrEF, pEF)
- Mean Right Atrial Pressure (mmHg)
- Systolic Right Ventricular Pressure (mmHg)

- Diastolic Right Ventricular Pressure (mmHg)
- Pulmonary arterial systolic pressure - RHC (mmHg)
- Diastolic Pulmonary-Artery Pressure (mmHg)
- Mean Pulmonary-Artery Pressure (mmHg)
- Mean Pulmonary Wedge Pressure (mmHg)
- Cardiac Output - RHC (L/min)
- Cardiac Index - RHC (L/min/m2)
- Pulmonary Vascular Resistance (PVR) (dyn.s/cm5)
- Cardiac output - ECHO (L/min)
- Left ventricular global longitudinal strain (%)
- Left ventricular stroke volume (mL)
- Left ventricular ejection fraction (%)
- Pulmonary arterial systolic pressure – ECHO (mmHg)
- Right ventricle / left ventricle ratio
- Right ventricular outflow tract acceleration time (ms)
- Systemic vascular resistance (dynes/s/cm-5)
- Tricuspid annular plane systolic excursion / pulmonary arterial systolic pressure ratio (cm/mmHg)
- Peak tricuspid regurgitation velocity (m/s)
- 6-minute walking distance (6MWD)
- Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS)
- Serum Creatinine (umol/L)
- NT-proBNP (pmol/L)
- Cystatin C (mg/dL)
- eGFR (mL/min/1.73m^2)

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. or later.

4.1.7.2 Presentation

Medical history and surgical history will be summarised for the FAS by treatment group and total. Summaries on participants' medical history will be produced by System Organ Class (SOC) and Preferred Term (PT).

By-study participant listings of all medical history and surgical history will be provided.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

For the purpose of inclusion in prior and/ or concomitant medication or therapy summaries, incomplete dates will be defined based on the rule of start and stop dates in Appendix A.1.

Prior medications are those taken prior to study intervention with a stop date prior to the first dose of study intervention.

Concomitant medications are those taken concurrently with investigational product regardless of the start date of the medication.

Initiation of loop diuretics during the study treatment period is defined as a start date of loop diuretics on or after the first dose date of study intervention and on or prior to the last dose date of study intervention. The categorization of loop diuretics will be based on the medical review of concomitant medications data (See Section 4.2.1.7).

4.1.8.2 Presentation

The number and percentage of participants who took prior and concomitant medications will be summarised by ATC classification codes and the generic term coded by WHO Drug Global B3 Sep 2022 or later for the FAS by treatment group and total. The number and percentage of participants who initiated loop diuretics during the study treatment period will be summarised by ATC classification codes and the generic term coded by WHO Drug Global B3 Sep 2022 or later for the FAS by treatment group and total.

By-study participant listings of all Prior and Concomitant medications will be provided.

Missing coding terms will be listed and summarised as “Not coded”.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated as:

((Actual number of completed injections)/(Expected number of injections)) × 100%

In this study, Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 are dosing visits. For study participants who complete all injections as planned, the expected number of injections is 12. For participants who prematurely discontinue treatment, the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

4.1.9.2 Presentation

Study treatment compliance will be calculated and summarized for the FAS.

Compliance will be summarized descriptively by treatment group and total. The number and percentage of study participants meeting certain compliance thresholds (0< number of injections < 3, 3 <= number of injections < 6, 6 <= number of injections < 9, 9 <= number of injections < 12, number of injections = 12) will also be reported. The administration of investigational product will be listed for the SS.

4.2 Endpoint Analyses

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

The primary estimand for primary and secondary endpoints are defined as follows:

Population of interest: FAS
Endpoint being assessed: Primary and secondary endpoints
Intercurrent event (ICE) and ICE strategy:
ICE: Discontinuations of study interventions for all reasons
Treatment policy strategy: Missing data after the ICE has occurred will be imputed using Wash-out approach (placebo multiple imputation). Further details can be found in Appendix A.2.
Summary measure being evaluated: Please refer to the table below for each endpoint.

The secondary estimand for the primary and secondary endpoint is defined as follows:

Population of interest: FAS
Endpoint being assessed: Primary and secondary endpoints
ICE and ICE strategy:
ICE: Discontinuations of study interventions for all reasons
Hypothetical strategy: All missing data will be excluded and be imputed using multiple imputation under MAR assumption. Further details can be found in Appendix A.2.
Summary measure being evaluated: Please refer to the table below for each endpoint.

For PK and exploratory endpoints, estimand will not be applied to and all observed data will be included in the analyses.

Table 2 Overview of primary and secondary endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To evaluate the effect of AZD3427 on PVR after 24 weeks of treatment in participants with HF and PH Group 2					
Primary estimand (applied to primary, sensitivity, and subgroup analysis)	Change in log-transformed PVR from baseline to Week 25 (>=Week 23[a]), as measured by Right heart catheterisation (RHC)	FAS for primary and subgroup analysis PPS for sensitivity analysis	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo with back-transformation to present the ratios of geometric least squares means.	4.2, 4.2.1, Appendix A.2
Secondary estimand		FAS	Hypothetical strategy		
Supplementary analysis		FAS	NA, no imputation will be performed on missing data.		
Objective 2: To evaluate the effect of AZD3427 on additional hemodynamic markers of cardiac function after 24 weeks of treatment in participants with HF and PH Group 2					
Primary estimand (applied to primary, sensitivity, and subgroup analysis)	Change from baseline to Week 25 (>=Week 23[a]) in RHC parameters. Parameters include: • mPAP and log-transformed pulmonary artery	FAS for primary and subgroup analysis PPS for sensitivity analysis (mPAP only)	Treatment policy strategy	mPAP: LS mean differences between each dose of AZD3427 and placebo PAWP: LS mean differences between each dose of AZD3427 and placebo with back	4.2, 4.2.2, 4.2.4, Appendix A.2

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary estimand	wedge pressure (PAWP).	FAS	Hypothetical strategy	transformation to present the ratios of geometric least squares means.	
Supplementary analysis		FAS (mPAP only)	NA, all postbaseline mPAP results are included.		
Primary estimand (applied to primary and subgroup analysis)	Change from baseline to Week 25 (>=Week 23[a]) in ECHO parameters Parameters include: • Cardiac output, SV, EF, LVGLS, PASP, RV/LV ratio, RVOT AT, TRV, TAPSE/PASP, • Systemic vascular resistance.	FAS for primary and subgroup analysis	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo	
Secondary estimand		FAS	Hypothetical strategy		
Supplementary analysis		FAS	NA, all postbaseline will be included and no imputation will be performed on missing data.		
Objective 3: To evaluate the effect of AZD3427 on function and symptoms after 24 weeks of treatment in participants with HF and PH Group 2					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary estimand (applied to primary and subgroup analysis)	Change in 6MWD and KCCQ-TSS from baseline to Week 25 (>=Week 23[a]).	FAS for primary and subgroup analysis	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo	4.2, 4.2.5, Appendix A.2
Secondary estimand		FAS	Hypothetical strategy		
Supplementary analysis	Change in KCCQ-TSS from baseline to Week 25 (>=Week 23[a]).	FAS	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo	

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary estimand	Change in NYHA FC from baseline to Week 25	FAS	Treatment policy strategy	Odds ratio of the relative AZD3427 treatment effect on NYHA FC improvement at Week 25 compared to placebo group	
Secondary estimand		FAS	Hypothetical strategy		
Objective 4: To evaluate the effect of AZD3427 on biomarkers of cardiac and renal function after 12 and 24 weeks of treatment in participants with HF and PH Group 2					
Primary estimand	Change in log-transformed serum creatinine, NT-proBNP, and cystatin C from baseline to Week 13 and Week 25.	FAS	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo with back transformation to present the ratios of geometric least squares means.	4.2, 4.2.5, Appendix A.2
Secondary estimand		FAS	Hypothetical strategy		
Primary estimand	Change in eGFR from baseline to Week 13 and Week 25.	FAS	Treatment policy strategy	LS mean differences between each dose of AZD3427 and placebo	

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary estimand		FAS	Hypothetical strategy		

Table 3 Overview of PK and exploratory endpoints

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Objective 5: To evaluate the PK of AZD3427 after repeat Q2W SC dosing in participants with HF and PH Group 2				
Secondary Endpoints	AZD3427 serum PK concentrations.	PKAS	Descriptive statistics of PK concentrations	4.3
Objective 6: To evaluate the effect of AZD3427 on the plasma proteome, and urine, serum and/or plasma biomarkers of inflammation, fibrosis, RAAS, tissue remodelling, fluid/electrolyte balance, and RXFP1 signalling after 12 and 24 weeks of treatment in participants with HF and PH Group 2 [b]				
Exploratory Endpoints	Change in log-transformed plasma and/or serum biomarkers from baseline to Week 13 and Week 25: • Renin, aldosterone, sodium, potassium, copeptin, serum osmolality, and erythropoietin. • hs-TnT, PIIINP, hsCRP, and PRO-C6. • TNF-α, TGF-β. • Plasma proteome through multiplex protein panel. • Endogenous plasma relaxin levels at baseline. Change in urine biomarkers from baseline to Week 13 and Week 25: • Sodium, potassium, and albumin-to-creatinine ratio. • Creatinine and KIM-1.	FAS	LS mean differences between AZD3427 and placebo with back-transformation to present the ratios of geometric least squares means	4.2.6
Objective 7: To evaluate the diagnostic accuracy of echocardiographic parameters to diagnose PH Group 2 based on RHC in the study population [b]				

Exploratory Endpoints	To evaluate the capability of echocardiographic parameters to diagnose of PH Group 2 based on RHC at baseline.	FAS	The aim of analysis is to find out which of the ECHO parameters and at what values jointly correspond to the diagnosis of RHC parameters (PAWP >= 15 mmHg and mPAP >= 20 mmHg).	4.2.7
Objective 8: To evaluate the effect of AZD3427 on CV outcomes				
Exploratory Endpoints	Time to CV death, HF hospitalisation, or outpatient visit due to HF deterioration from randomisation to Week 25.	FAS	Kaplan-Meier (KM) estimate by treatment group, difference in KM estimate between treatment groups and hazard ratio (HR) between treatment groups	4.2.94.2.8
Objective 9: To evaluate the effect of AZD3427 on clinical outcomes				
Exploratory Endpoints	• Clinical benefit at Week 25, consisting of a composite of all-cause death, HF hospitalisations, outpatients visit due to HF deterioration and change from baseline at Week 25 in 6MWD and change from baseline at Week 25 in KCCQ-TSS, assessed using a 'win-ratio' approach. • • Change in KCCQ CSS and OSS from baseline to Week 25.	FAS	The win ratio and 95% confidence interval for win ratio of each treatment group	4.2.9

[a] For participants who have missing PVR at Week 25 and have the post-baseline measures on or after Week 23, the measures will be used in the analysis regardless of completion of study intervention.

[b] Results of each of these exploratory biomarker analyses may or may not be included in the CSR of this study.

4.2.1 Primary Endpoint

The primary endpoint is change in PVR from baseline to Week 25.

4.2.1.1 Definition

PVR will be assessed by right heart catheterization at baseline and Week 25 (on or after Week 23: Study Day on or after day 148 based on the analysis visit window). The primary estimand attributes are defined in Section 4.2. The primary clinical question of interest is: What is the back transformed least square means difference (geometric mean ratio) of change in log-transformed PVR from baseline to Week 25 in FAS treated with each dose of AZD3427 vs placebo regardless of adherence to the study intervention?

4.2.1.2 Derivations

PVR will be collected in RAVE for visits presented in CSP Table 1 and log-transformed prior to statistical analysis. PVR will be automatically calculated in RAVE using the following formula: PVR (dyn.s/cm5) = 80* [mPAP (mmHg) – PAWP (mmHg)] / Cardiac output (L/min).

4.2.1.3 Handling of Dropouts and Missing Data

Missing data will be handled in accordance with the estimands detailed in Section 3.3.3, Section 4.2, and Appendix A.2.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary objective will be assessed through a primary estimand.

Log transformed ratio to baseline in PVR at Week 25 will be analysed using an ANCOVA model, with treatment as fixed effect, stratification factor (i.e. China and Japan, or others) fitted as categorical covariates and log-transformed baseline PVR fitted as a continuous covariate.

The point estimate and 95% CI will be back transformed onto the original scale.

An over time table and a by-participant listing will be provided for results of RHC.

4.2.1.5 Secondary Analyses of the Primary Endpoint

The secondary estimand attributes are defined in Section 4.2. The secondary clinical question of interest is: What is the back transformed least square means difference (geometric mean ratio) of change in log-transformed PVR from baseline to Week 25 in FAS treated with each dose of AZD3427 vs placebo would have completed the study intervention? The imputation algorithm is outlined in section 3.3.4, Section 4.2, and Appendix A.2. The same ANCOVA model used for the primary estimand will be utilized here.

4.2.1.6 Sensitivity Analyses of the Primary Endpoint

Additional analysis will be conducted using the same ANCOVA model in section 4.2.1.4 for the primary estimand detailed in Table 2 and change the analysis population to PPS.

4.2.1.7 Subgroup Analysis

The treatment effect within each subgroup category will be estimated by fitting the same statistical model as for the primary analysis described in Section 4.2.1.4 to each subgroup category using the primary estimand.

The same statistical model, adding the subgroup variable as explanatory variable and a subgroup-by-treatment interaction term will be fitted to each subgroup.

Subgroup analysis will be performed when the number of participants per treatment group per level is greater than 5.

A forest plot displaying geometric mean ratio and 95% confidence intervals by subgroups using ANCOVA model will be presented. The comparisons of each dose of AZD3427 versus placebo, total pooled AZD3427 and placebo, and high pooled AZD3427 and placebo will be included into the forest plot.

Subgroup variables are defined below:

- NYHA FC (II, III+IV)
- Age (Above, below 65)
- Sex (Male/female)
- Race (As captured in eCRF)
- Left ventricular ejection fraction (LVEF) (Median/<50%, >=50)
- NT-proBNP (<Median, >=Median)
- Type 2 diabetes at baseline (Yes, No)
- BMI (<30, >=30)
- Baseline eGFR (<60, >=60)
- mPAP (<Median, >=Median)
- PVR (<Median, >=Median)
- PAWP (<Median, >=Median)
- Cardiac index (<Median, >=Median)
- Concomitant medications 1 (iron supplementation)
- Concomitant medications 2 (SGLT2i)
- Concomitant medications 3 (Raas (ACE/ARB))
- Concomitant medications 4 (Entresto)
- Concomitant medications 5 (Mineralocorticoid receptor antagonist (MRA))
- Concomitant medications 6 (Diuretics)
- Concomitant medications 7 (Loop diuretics)
- Concomitant medications 8 (Beta blockers)
- Concomitant medications 9 (Thiazide diuretics)

The categorization of subgroup of concomitant medications 1 to 9 will be based on the medical review of concomitant medications data in RAVE.

4.2.1.8 Supplementary Analysis

A supplementary analysis will be conducted using the same ANCOVA model in section 4.2.1.4 with participants who completed assessment and have no missing post-baseline PVR. No ICE and estimand will be considered.

4.2.2 Secondary Endpoint – RHC parameters

Change from baseline to Week 25 (defined as assessments on or after Week 23: Study Day on or after day 148 based on the analysis visit window) in mPAP and log-transformed PAWP will be analysed.

4.2.2.1 Definition

Primary and secondary estimands in Section 4.2 will be applied to the endpoint of RHC parameters.

4.2.2.2 Derivations

Measurements of RHC parameters will be collected in RAVE at baseline and Week 25 according to CSP SoA. Measurements of PAWP will be log-transformed for statistical analysis purposes.

4.2.2.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data will use the same approach as described for primary efficacy endpoint in Section 4.2.1.3. Details can also be found in Section 3.3.4 and Appendix A.2.

4.2.2.4 Primary Analysis of Secondary Endpoint

The analysis for RHC parameters, i.e. mPAP and PAWP, will use the same approach as described for primary efficacy endpoint in Section 4.2.1.4.

An over time table and a by-participant listing will be provided for results of RHC parameters.

4.2.2.5 Secondary Analysis of Secondary Endpoint

The analysis for RHC parameters, i.e. mPAP and PAWP, will use the same approach as described for primary efficacy endpoint in Section 4.2.1.5.

4.2.2.6 Sensitivity Analyses of the Secondary Endpoint

The analysis for mPAP will use the same approach as described for primary efficacy endpoint in Section 4.2.1.4 using the primary estimand and change the analysis population to PPS.

4.2.2.7 Subgroup Analysis

Subgroup analysis specified in section 4.2.1.7 will be repeated based on the primary analysis of mPAP.

4.2.2.8 Supplementary Analyses of the Secondary Endpoint

A supplementary analysis will be conducted for mPAP using the same model in Section 4.2.1.4 with participants who completed assessment and have no missing post-baseline mPAP.

4.2.3 Secondary Endpoint – Echocardiographic parameters

Echocardiographic parameters

Change from baseline to Week 25 in echocardiographic (ECHO) parameters will be analysed. The following parameters will be included: Cardiac output (CO), left ventricular stroke volume (LV SV), left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LV GLS), right ventricle / left ventricle (RV/LV) ratio, right ventricular outflow tract acceleration time (RVOT AT), peak tricuspid regurgitation velocity (TRV), pulmonary arterial systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE)/PASP, systemic vascular resistance (SVR).

4.2.3.1 Definition

Primary and secondary estimands in Section 4.2 will be applied to the endpoint of ECHO parameters.

4.2.3.2 Derivations

ECHO parameters will be measured by central echo core lab at baseline and Week 25 according to CSP SoA.

4.2.3.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data will use the same approach as described for primary efficacy endpoint in Section 4.2.1.3. Details can also be found in Section 3.3.4 and Appendix A.2.

4.2.3.4 Primary Analysis of Secondary Endpoint

The analysis for the ECHO parameters will also use the same approach as described for primary efficacy endpoint in section 4.2.1.4, except no log-transformation in the data derivations.

An over time table and a by-participant listing will be provided for results of ECHO parameters.

4.2.3.5 Secondary Analysis of Secondary Endpoint

The analysis for the ECHO parameters will also use the same approach as described for primary efficacy endpoint in section 4.2.1.5, except no log-transformation in the data derivations.

4.2.3.6 Subgroup Analysis

Subgroup analysis specified in section 4.2.1.7 will be repeated based on the primary analysis of ECHO parameters (LVEF only).

4.2.3.7 Supplementary Analyses of the Secondary Endpoint

A supplementary analysis will be conducted for ECHO parameters using the same model in Section 4.2.1.4 with participants who completed assessment and have no missing post-baseline ECHO parameters.

4.2.4 Secondary Endpoint – 6MWD, KCCQ-TSS, and NYHA FC

Change in 6MWD, KCCQ-TSS, and NYHA FC from baseline to Week 25 (defined as assessments on or after Week 23: Study Day on or after day 148 based on the analysis visit window) are secondary endpoints.

4.2.4.1 Definition

Primary and secondary estimands in Section 4.2 will be applied to the endpoint of 6MWD, KCCQ-TSS, and NYHA.

4.2.4.2 Derivations

6MWD

6MWD will be collected in the 6-minute walking test in RAVE at baseline and Week 25 according to CSP SoA.

NYHA FC

NYHA FC will be collected in the NYHA – Heart Failure form in RAVE according to CSP SoA.

KCCQ-TSS

KCCQ will be collected in RAVE and the calculations of summary scores are included in Appendix B Calculations of summary scores of KCCQ.

4.2.4.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data of 6MWD and KCCQ-TSS will use the same approach as described for primary efficacy endpoint in Section 4.2.1.3. Details can also be found in Section 3.3.4 and Appendix A.2.

4.2.4.4 Primary Analysis of Secondary Endpoint

The primary analysis of 6MWD use the same approach as described for ECHO parameters in Section 4.2.3.4.

The scale of KCCQ-TSS scores range from 0-100, KCCQ-TSS scores are assumed to follow a beta distribution after dividing by 100. The beta regression will be used for the analysis for KCCQ-TSS. KCCQ-TSS at week 25 will be the dependent variables and

baseline and treatment*baseline interaction, and stratification factor as independent variable.

Shift tables will be used to present NYHA FC shift from baseline (categorized as NYHA class II, III, and IV) to Week 25 (categorized as NYHA class I, II, III, and IV). A summary table of NYHA FC improvement (class IV to III/II/I, class III to II/I, and class II to I), worsening (class II to III/IV, class III to IV), and no change (class II to II, class III to III, and class IV to IV) from baseline to Week 25 will be presented. The analysis for NYHA FC will be based on the logistic regression, which NYHA FC change from baseline to week 25 (improve, no change, worsen) will be the dependent variable, treatment group will be the independent variable, and stratification factor fitted as categorical covariates. The odd ratios of improve vs not improve, and worsen vs not worsen of each of AZD3427 dose compared to placebo will be presented.

Over time tables and by-participant listings will be provided for results of 6MWD, KCCQ and NYHA FC.

4.2.4.5 Secondary Analysis of Secondary Endpoint

The analysis for the 6MWD, KCCQ-TSS, and NYHA FC will also use the same approach as described for ECHO parameters in Section 4.2.3.5.

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

A supplementary analysis for mean changes in KCCQ-TSS at Week 25 will use the same approach as described for the primary analysis of ECHO parameters in Section 4.2.3.4, an interaction term of baseline*treatment will be included in the model.

4.2.4.7 Subgroup Analysis

Subgroup analysis of mean changes in 6MWD and relative change in KCCQ-TSS will be performed similarly to Section 4.2.1.7.

4.2.5 Secondary Endpoint – Serum creatinine, NT-proBNP, cystatin C, and eGFR

Change in eGFR and log-transformed serum creatinine, NT-proBNP, cystatin C from baseline to Week 13 and Week 25 compared with placebo are secondary endpoints.

4.2.5.1 Definition

Primary and secondary estimands in Section 4.2 will be applied to the endpoint of Serum creatinine, NT-proBNP, cystatin C, and eGFR.

4.2.5.2 Derivations

Results of serum creatinine, cystatin C, and eGFR will be collected from central lab for baseline, Week 1, Week 3, Week 5, Week 7, Week 13, Week 19, and Week 25 visits presented in CSP SoA. eGFR will be calculated by central lab using CKD-EPI equation (Levey et al 2009) and transferred from central lab. Results of NT-proBNP will be collected from central lab for baseline, Week 1, Week 7, Week 13, Week 19, and Week 25.

Measurements of serum creatinine, NT-proBNP, cystatin C will be log-transformed for statistical analysis purposes.

4.2.5.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data will use the same approach as described for primary efficacy endpoint in Section 4.2.1.3. Details can also be found in Section 3.3.4 and Appendix A.2.

4.2.5.4 Primary Analysis of Secondary Endpoint

The changes in log-transformed serum creatinine, NT-proBNP, and cystatin C and the change in eGFR from baseline at Week 25 will be analysed using an MMRM model. The model will include all the subjects in FAS with treatment, stratification factor, visit, and treatment-by-visit interaction as fixed effects and baseline result as covariate, subject as the random effect. An unstructured covariance structure will be used to model the within-participant error variance. If the model fails to converge, then a homogeneous compound symmetry matrix will be used. Kenward-Roger method will be used as degrees of freedom method. The comparison of each dose of AZD3427 versus placebo will be based on the geometric mean ratio (serum creatinine, NT-proBNP, and cystatin C) and least squares mean difference (eGFR).

Line plots for change in serum creatinine, NT-proBNP, cystatin C, and eGFR from baseline over time will be presented by each treatment group, for all participants in FAS.

Over time tables and by-participant listings will be provided for results of serum creatinine, NT-proBNP, cystatin C, and eGFR.

4.2.5.5 Secondary Analysis of Secondary Endpoint

The analysis for serum creatinine, NT-proBNP, cystatin C, and eGFR, will use the same approach as described for primary efficacy endpoint in Section 4.2.1.5.

4.2.6 Exploratory Endpoint – Plasma, serum, and urine biomarkers

4.2.6.1 Definition

Plasma and serum biomarkers

Change in plasma and serum biomarkers from baseline to Week 13 and Week 25:

- Renin, aldosterone, sodium, potassium, copeptin, serum osmolality, and erythropoietin.
- hs-TnT, PIIINP, hsCRP, and PRO-C6.
- TNF-α, TGF-β.
- Plasma proteome through multiplex protein panel (eg, Olink® Explore).

Baseline assessment:

- Endogenous plasma relaxin levels.

Urine biomarkers

Change in urine biomarkers from baseline to Week 13 and Week 25:

- Sodium, potassium, and albumin-to-creatinine ratio.
- Creatinine and KIM-1.

The results of each of these exploratory biomarker analyses may or may not be included in the CSR of this study.

4.2.6.2 Derivations

Plasma, serum, and urine biomarkers will be collected from central laboratory for visits presented in CSP SoA. Measurements of plasma, serum, and urine biomarkers will be log-transformed for statistical analysis purposes.

4.2.6.3 Handling of Dropouts and Missing Data

Missing data of plasma, serum, and urine biomarkers will not be imputed.

4.2.6.4 Primary Analysis of Exploratory Endpoint

The analysis for plasma, serum, and urine biomarkers will use the same approach as described for serum creatinine, NT-proBNP, and cystatin C in Section 4.2.5.4.

Over time tables and by-participant listings will be provided for results of plasma, serum, and urine biomarkers.

4.2.7 Exploratory Endpoint – capability of echocardiographic parameters to diagnose of PH Group 2

4.2.7.1 Definition

The capability of echocardiographic parameters at baseline to diagnose of PH group 2 will be defined as the relationship between echocardiographic parameters and PH group 2 defined as PAWP >= 15mmHg and mPAP >= 20 mmHg.

4.2.7.2 Derivations

Echocardiographic parameters will be collected in the visits according to CSP SoA.

4.2.7.3 Handling of Dropouts and Missing Data

Missing data of echocardiographic parameters will not be imputed.

4.2.7.4 Primary Analysis of Exploratory Endpoint

The aim of analysis is to find out which of the ECHO parameters and at what values jointly correspond to the diagnosis of RHC parameters (PAWP >= 15 mmHg and mPAP >= 20 mmHg). Additional details of this exploratory analysis may be documented in a separate analysis plan.

4.2.8 Exploratory Endpoint – Time to cardiovascular death, HF hospitalisation, or outpatient visit due to HF deterioration

4.2.8.1 Definition

Time to cardiovascular (CV) death, HF hospitalisation, or outpatient visit due to HF deterioration from randomisation to Week 25 will be calculated.

CV death is defined as the adverse event on the eCRF death details form where the primary cause of death is CV death or unknown cause of death.

The information of HF hospitalisation will be collected in Heart Failure Event form.

The information of outpatient visit due to HF deterioration will be collected in Heart Failure Event form (Urgent heart failure visit).

4.2.8.2 Derivations

Time to CV death, HF hospitalisation, or outpatient visit due to HF deterioration (defined in 4.2.8.1) from randomisation to Week 25 will each be calculated as:

Time to event (days) = (Date of event – Date of first study drug administration) + 1

Event represents CV death, HF hospitalisation, or outpatient visit due to HF deterioration (Urgent heart failure visit) (defined in 4.2.8.1) respectively.

4.2.8.3 Handling of Dropouts and Missing Data

Missing data will be handled by the rules of censor in Table 4 Rules of event and censor.

4.2.8.4 Primary Analysis of Exploratory Endpoint

Time to first occurrence of CV death, HF hospitalisation, or outpatient visit due to HF deterioration (defined in 4.2.8.1) will be estimated using the Kaplan- Meier product-limit method for each treatment group. The rule of event/censor is listed below. Cox proportional hazard model with Efron's method of tie handling will be used with treatment group as a factor and stratification factor (i.e. China and Japan, or others) fitted as categorical covariates. Treatment effect will be estimated by hazard ratio. The analysis will be repeated using total and high pool AZD3427 as treatment groups. The 95% confidence interval and p-value will be displayed based on Wald statistic.

Table 4 Rules of event and censor

Situation	Date of event or censoring	Outcome
Participant with CV death/HF hospitalisation/ outpatient visit due to HF deterioration (defined in 4.2.8.1) in treatment period	Date of CV death/Start date of HF hospitalisation/Start date of outpatient visit due to HF deterioration (defined in 4.2.8.1), whichever comes first	Event
Participant with no post-Baseline visit in Treatment Period	Date of first study drug administration	Censor
Participant who discontinues IMP prior to the event CV death/HF	Date of the last visit on or prior to the date of IMP discontinuation	Censor

hospitalisation/outpatient visit due to HF deterioration (defined in 4.2.8.1) in treatment period		
Participant who is lost to follow-up prior to the event CV death/HF hospitalisation/outpatient visit due to HF deterioration (defined in 4.2.8.1) in treatment period	Date of the last visit on or prior to the date of lost to follow-up	Censor
Participant who completes the treatment period without observing an event	Date of the last visit in the Treatment Period	Censor

The median time to CV death, HF hospitalisation, or outpatient visit due to HF deterioration (defined in 4.2.8.1) and the number of participants experienced events will be calculated and presented for each treatment group. Kaplan-Meier estimate at Day 85 (Week 13) including 95% CI will be calculated and presented for each treatment group. Kaplan-Meier plots of time to CV death, HF hospitalisation, or outpatient visit due to HF outpatient (defined in 4.2.8.1) will also be provided by treatment group.

4.2.9 Exploratory Endpoint – Clinical benefit at Week 25, consisting of a composite of all-cause death, HF hospitalisations, outpatient visit due to HF deterioration and change from baseline at Week 25 in KCCQ-TSS/6MWD

4.2.9.1 Definition

The unmatched win-ratio approach will be used for this composite endpoint.

4.2.9.2 Derivations

The general principle behind the win ratio is as follows. One first forms every possible participant-to-participant pair: that is, every participant in the AZD3427 treatment groups is compared with every participant in the placebo treatment group. Then, within each pair one evaluates the component outcomes in descending order of importance until one of the pair shows a better outcome compared with the other. If the participant on the AZD3427 has the better outcome it is called a ‘win’ and receive a +1 score, whereas if the placebo participant does better it is a ‘loss’ and receive a 0 score. Otherwise, it is a ‘tie’ and receive a 0 score. The order of component outcomes is listed below:

- All-cause of death
- HF hospitalizations
- Outpatient visit due to HF deterioration (defined in 4.2.8.1)
- Change from baseline at Week 25 in KCCQ-TSS/6MWD

Below is the general principle behind the win ratio approach:

Table 5 Principles of win ratio approach

Comparison of each potential participant pair (one from AZD3427 and one from placebo)	How event is assessed
Step 1	

If one or both participants die:	
Participant in AZD3427 group dies first	Placebo wins
Participant in placebo group dies first	AZD3427 wins
Both participants die on the same day	Go to Step 2
If neither of the participants die	Go to Step 2
Step 2	
If no ranking yet available	
Participant in AZD3427 group had more HF hospitalizations	Placebo wins
Participant in placebo group had more HF hospitalizations	AZD3427 wins
Both participants were hospitalized equal number of times	Go to Step 3
Neither of the participants was hospitalized for heart failure	Go to Step 3
Step 3	
If no ranking yet available	
Participant in AZD3427 group had more outpatient visits due to HF deterioration	Placebo wins
Participant in placebo group had more outpatient visits due to HF deterioration	AZD3427 wins
Both participants had equal number of times of outpatient visits due to HF deterioration	Go to Step 4
Neither of the participants has outpatient visits due to HF deterioration	Go to Step 4
Step 4	
If no ranking yet available	
Participant in AZD3427 group had no change >= 20 m in 6MWD from baseline at Week 25 and Participant in placebo group had a change >=20m in 6MWD from baseline at week 25	Placebo wins
Participant in placebo group had no change >= 20 m in 6MWD from baseline at Week 25 and Participant in AZD3427 group had a change >=20m in 6MWD from baseline at week 25	AZD3427 wins
Both participants had no change >=20m in 6MWD from baseline at Week 25, or both participants had changes >= 20 m in 6MWD from baseline at Week 25	Go to Step 5
Step 5	
If no ranking yet available	
Participant in AZD3427 group had no change >= 5 points in KCCQ-TSS from baseline at Week 25 and Participant in placebo group had a change >=5 points in KCCQ-TSS from baseline at week 25	Placebo wins
Participant in placebo group had no change >= 5 points in KCCQ-TSS from baseline at Week 25 and Participant in AZD3427 group had a change >=5 points in KCCQ-TSS from baseline at week 25	AZD3427 wins
Both participants had no change >=5 points in KCCQ-TSS from baseline at Week 25, or both participants had changes >= 5 points in KCCQ-TSS from baseline at Week 25	Tie

4.2.9.3 Handling of Dropouts and Missing Data

Missing data will not be imputed for the win-ratio approach.

4.2.9.4 Primary Analysis of Exploratory Endpoint

In the unmatched win ratio approach, every participant in each AZD3427 group (1.1, 5.4, 30.0 mg), high pooled, and total pooled is compared with every participant in the placebo group. Specifically, let $N_{AZD3427\ 1.1mg}$ and $N_{Placebo}$ be the number of participants in the AZD3427 1.1 mg and Placebo group, respectively, then we make $N_{AZD3427\ 1.1mg} \times N_{Placebo}$ paired comparisons. The win ratio (RW) is then calculated as:

$$RW = \frac{N_W}{N_L}$$

where N_W and N_L are the total number of pairwise wins and losses, respectively, for the AZD3427 1.1 mg group. 95% CI and p-value will be calculated based on the generalized analytic solution introduced by Dong. The detailed calculation can be found in Appendix C Calculations of confidence interval and p-value of win ratio

An approximate 95% confidence interval will be calculated as follows.

From the win ratio RW one calculates $\log RW$. Then an approximate standard error for $\log RW$ is $s = \log RW / z$, the standardised normal deviate obtained for the above significance test. Then the 95% confidence interval for $\log RW$ is $\log RW \pm 1.96 \times s$. One then exponentiates these confidence limits to obtain the 95% confidence limits for RW. The win ratio and 95% confidence interval for win ratio will be presented by each treatment group.

4.2.10 Exploratory Endpoint – Change in KCCQ-CSS and OSS from baseline to Week 25

4.2.10.1 Definition

Primary and secondary estimands in Section 4.2 will be applied to the endpoint of KCCQ-CSS/OSS.

4.2.10.2 Derivations

KCCQ will be collected in RAVE and the calculations of summary scores are included in Appendix B Calculations of summary scores of KCCQ.

4.2.10.3 Handling of Dropouts and Missing Data

The handling of dropouts and missing data will be the same as KCCQ-TSS in Section 4.2.4.3.

4.2.10.4 Primary Analysis of Exploratory Endpoint

KCCQ-CSS/OSS will be analysed similarly to KCCQ-TSS in Section 4.2.4.4.

Over time tables and by-participant listings will be provided for results of KCCQ-CSS/OSS.

4.2.10.5 Subgroup Analysis

Subgroup analysis of relative changes in KCCQ-CSS/OSS will be performed as described in Section 4.2.1.7.

4.2.11 Exploratory Endpoint – RHC parameters

4.2.11.1 Definition

Change from baseline to Week 25 (defined as assessments on or after Week 23: Study Day on or after day 148 based on the analysis visit window) Mean Right Atrial Pressure, Systolic Right Ventricular Pressure, Diastolic Right Ventricular Pressure, Pulmonary

arterial systolic pressure, Diastolic Pulmonary-Artery Pressure, and Cardiac Output will be analysed.

4.2.11.2 Derivations

Exploratory RHC parameters will be measured at baseline and Week 25 according to CSP SoA.

4.2.11.3 Handling of Dropouts and Missing Data

Missing data of exploratory RHC parameters will not be imputed.

4.2.11.4 Primary Analysis of Exploratory Endpoint

The analysis for the exploratory RHC parameters will also use the same approach as described for primary efficacy endpoint in section 4.2.1.4, except no log-transformation in the data derivations.

4.2.12 Exploratory Endpoint – Echocardiographic parameters

4.2.12.1 Definition

Change from baseline to Week 25 in echocardiographic (ECHO) parameters will be analysed. The following parameters will be included: left ventricular end diastolic volume (LV EDV), LV end-diastolic volume index (LV EDVi), left ventricular end systolic volume (LV ESV), LV end-systolic volume index (LV ESVi), left ventricular stroke volume index (LV SVi), left ventricular mass index, maximal left atrial volume index (LAVi max), minimal left atrial volume index (LAVi min), left atrial emptying fraction, left atrial reservoir strain (LARS), early mitral filling velocity/early diastolic mitral annular velocity (E/E'), right atrial (RA) area, tricuspid annular plane systolic excursion, RV end-diastolic area (RV EDA), right ventricular area systole, RV fractional area change (RV FAC), RV global longitudinal strain, right ventricular (RV) free wall strain, RV FAC/ PASP, RV global longitudinal strain/PASP, RV free wall strain/PASP will be analysed.

4.2.12.2 Derivations

Exploratory ECHO parameters will be measured by central echo core lab at baseline and Week 25 according to CSP SoA.

4.2.12.3 Handling of Dropouts and Missing Data

Missing data of exploratory ECHO parameters will not be imputed.

4.2.12.4 Primary Analysis of Exploratory Endpoint

The analysis for the exploratory ECHO parameters will also use the same approach as described for primary efficacy endpoint in section 4.2.1.4, except no log-transformation in the data derivations.

4.3 Pharmacokinetics

Concentration Listings:

Pharmacokinetic concentration data will be listed by dose level, PK Day/Visit, and participant for the SS. Concentration listings will include nominal PK sampling time, actual

sampling times relative to dose administration, deviation from nominal time, and concentration. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and considered excluded from PK analysis.

Concentration Summary Tables:

Concentration will be summarized by dose level, and PK Day/Visit for the PKAS. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: N, n, n<LLOQ, arithmetic mean, SD, geometric mean, geometric SD (calculated as: $exp(\log(sd))$) , geometric CV% (calculated as: $gCV\% = SQRT(e^{s^2} - 1) \times 100$; where s is the SD of the log transformed values), median, minimum, and maximum values.

Concentrations that are BLQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly. (This does not affect values in listings or in individual concentration plots.)
- At a time point where more than 50% (but not all) of the values are NQ, the gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.
- Three observations > LLOQ are required as a minimum for a serum concentration to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

Concentration Figures:

Figures for the geometric meaNArithmetic mean concentration-time data (±gSD/SD error bars) will be presented by treatment group (1.1, 5.4 and 30 mg), for all participants in the PKAS on both linear and semi-logarithmic scales using protocol scheduled times. BLQ values will be handled as described for the Concentration Summary Tables.

Individual concentration-time data will be graphically presented on linear and semi-logarithmic scales both by subject and by treatment group, for PKAS. Concentrations that are BLQ will be regarding as missing, except for pre-dose BLQ values on Day 1 of dosing, which will be set to 0 for linear scale plots.

Scatter plot of dose normalized individual geometric mean concentration of AZD3427 versus baseline covariates will be presented by baseline covariate (body weight and eGFR). Individual dose normalized geometric mean concentration will be calculated based on the serum concentration data from the Week 13, 19, 25. Scatter plots should also include a linear regression line for the log-transformed data, hence a line according to Y= alpha+exp(beta) where alpha and beta are the regression line parameters for log(individual geometric mean concentration) = alpha + beta*log(baseline covariate).

4.4 Immunogenicity

4.4.1 Evaluation of ADA Impact on PK, PD, Efficacy, and Safety

The impact of ADA on PK, PD, and safety may be evaluated by stratifying serum trough concentrations (C_{trough}) of AZD3427, selected PD biomarker levels, selected clinical efficacy endpoints, and safety measures by subject ADA status and titer quartiles (where appropriate), summarized using typical descriptive statistics, and presented graphically and/or in tables. Efficacy measures to be stratified by subject ADA status will include but may not be limited to PVR, mPAP, and PAWP.

Summaries of adverse Events (AEs) will be presented by the subgroups of ADA negative, TE-ADA positive, non-TE-ADA positive. Summaries will include AEs, serious adverse events (SAEs), SAEs with outcome death, AEs leading to discontinuation of IP, AEs and SAEs assessed as possibly related by the investigator, injection site reaction, hypersensitivity, and hypersensitivity assessed by PI.

Lastly, impact of ADA (e.g., based on antibody titer, onset of ADA, subjects with treatment-emergent ADA vs. non-treatment-emergent ADA etc.) on C_{trough} and selected efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

ADA will be summarized as categorical variables with the number and percentages with a positive result at the specific visit. Immunogenicity titer will be summarized descriptively as continuous variable, only for ADA positive tests, with median, Q1, Q3, minimum, and maximum, at each analysis visit.

ADA will be also summarized including the following:

• ADA prevalence: subjects who are ADA positive at any visit (including baseline)

• Subjects who are ADA positive at baseline only

• Subjects who are not ADA positive at baseline and have at least one positive value postbaseline only (treatment-induced ADA)

• Subjects who are persistently positive; persistently positive is defined as not positive at baseline and at least 2 post baseline ADA positive measurements (with >= 16 weeks apart) or an ADA positive result at the last available assessment

• Proportion of subjects who are transiently positive; transiently positive is defined as not positive at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive

• Proportion of subjects who are treatment-boosted ADA; treatment-boosted ADA is defined as baseline ADA titer that was boosted to a 4-fold or higher level following drug administration

• ADA incidence (TE-ADA), defined as the sum of treatment-induced ADA (post-baseline positive only) and treatment-boosted ADA.

• Non-TE ADA, defined as ADA positive but not fulfilling the definition of TE-ADA positive.

• Both baseline and post-baseline positive, defined as ADA positive at baseline and at least one post-baseline ADA positive.

For the presentation of ADA results at a single time point (e.g. baseline or by visit summaries), the corresponding titre summary will be based on the titres of the positive samples for that particular visit. For the presentation of ADA results across visits (e.g. any post-baseline), the corresponding titre summaries will be based on the maximum titre of all positive samples for each participant. Titres of positive measurements reported as <=50 (minimum required dilution) will be imputed as 50.

The number and percentage of participants with NAbs will also be summarized, if applicable. The presence of NAbs will be tested in all ADA-positive samples using a ligand binding assay. The following variables will be evaluated:

- Proportion of participants with at least one non-missing ADA result (at any time) who are NAbs positive at any time
- Proportion of participants with a non-missing ADA result (at a specific visit) who are NAbs positive by visit

A by-participant listing of ADA/NAbs results for the SS will be presented.

4.5 Safety Analyses

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

Tables are provided for the SS, listings are provided for All participants or the SS depending on the availability of data.

The aim of the analyses of safety data is to assess the general safety objective, evaluated in a scenario where study treatment is not prematurely discontinued.

Unless specified otherwise, safety data is presented by the on-study period.

4.5.1 Exposure

4.5.1.1 Definitions and Derivations

Definition for duration of exposure during the treatment period is provided as follows:

Duration of exposure (days) = (Date of last dose – date of first dose) + 14 days

The use of +14 days reflects the dosing interval of two weeks.

4.5.1.2 Presentation

Descriptive summary of duration of exposure will be provided.

4.5.2 Adverse Events

4.5.2.1 Definitions and Derivations

The MedDRA (version 28.0 at a minimum) will be used to code AEs.

Summary tables of AE will include AEs on or after the date of randomisation up to and including the date of last clinical event assessment, unless the participant dies while under follow-up, then the date of death is taken as the end of the period. If a participant withdraws consent to continue in the study, then the on-study analysis period ends on this date at the latest.

Severity

In summaries including severity, the following intensity categories will be summarized: ‘Mild’, ‘Moderate’, ‘Severe’. Participants who experience the same event multiple times will be included in the most severe category reported. Events with missing intensity will be considered as ‘Severe’ events for summary purposes but recorded as missing in the listings.

Relationship (causality)

The following relationships will be summarized: ‘Not related’, ‘Related’. If at any time the AE is assessed as related, it will be regarded as related. Events with missing relationship will be considered as ‘Related’ to the last given study drug for summary purposes but recorded as missing in the listings.

Most common AEs

Most common AEs will be defined as adverse events occurring in more than 5% of participants in any treatment group.

4.5.2.2 Presentation

An overview of AEs will be presented for each treatment group including the number and percentage of participants with any AE, AEs with outcome of death, serious AEs (SAEs), and discontinuation due to AE (DAE) of study intervention, AEs leading to withdrawal from the study, as well as the number of individual occurrences in those categories.

Separate AE tables will be provided by treatment groups as follows:

- Number and percentage of subjects with any AE by SOC and PT
- Event count of all AEs by SOC and PT
- Overview of subjects with any AE by AZD3427 anti-drug antibody category
- Number and percentage of subjects with any AE by AZD3427 anti-drug antibody category, by SOC, and PT
- Number and percentage of subjects with any AE assessed by investigator as possibly related to investigational product by SOC and PT
- Number and percentage of subjects with any AE by maximum reported intensity by SOC and PT
- Number and percentage of subjects with any SAE by SOC and PT
- Number and percentage of subjects with any possibly related SAE by SOC and PT
- Number and percentage of subjects with AE with outcome of death by SOC and PT
- Number and percentage of subjects with any AE leading to discontinuation of investigational product by SOC and PT
- Number and percentage of subjects with any AE leading to withdrawal from study by SOC and PT
- Number and percentage of subjects with most common AEs (frequency of more than 5%) by SOC and PT
- Number and percentage of subjects with any non-serious AEs occurring in more than 5% of participants by SOC and PT– FDAAA requirement
- Number and percentage of subjects with any AEs sorted by decreasing frequency on preferred term level
- Key participants information for participants with AEs with outcome of death
- Key participants information for participants with SAE
- Key participants information for participants with DAE
- Number and percentage of subjects with any injection site reactions by SOC and PT
    - Injection site reactions are defined as all AEs checked as ISRs in the eCRF "Adverse Event" and/or AEs with HLT "Injection Site Reaction"
- Number and percentage of subjects with any hypersensitivity reaction by SOC and PT

  - Hypersensitivity is defined as all AEs with SMQs “Anaphylactic reaction” (Narrow) and/or “Hypersensitivity reactions” (Narrow)
- Number and percentage of subjects with any AE checked as “hypersensitivity reaction” in the eCRF “Adverse Event”
- Key participants information for participants with injection site reactions
- Key participants information for participants with hypersensitivity reactions assessed by Principal Investigator

A by-participant listing of all AEs including SAEs occurred prior to date of randomisation for the SS will be presented, and A by-participant listing of all deaths that occurred during the study will be provided. A by-participant listing for all AEs in ADA positive subjects. A by-participant listing of AEs for participants who received incorrect investigational treatment will be provided.

4.5.3 Clinical Laboratory, Blood Sample

4.5.3.1 Definitions and Derivations

Laboratory parameters will be presented for each treatment group. Any laboratory parameters with results from the laboratory given as “<xx” or “>xx” will be imputed with the absolute value of the number without the sign (eg, < 2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

Laboratory variables that will be measured are detailed in CSP Table 5.

Treatment emergent haemaotology and chemistry abnormalities will be defined as Table 5. Treatment emergent abnormalities will be based on assessments after first dose of investigational product up to and including safety follow-up visit.

Table 5 Treatment-emergent haemotology and chemistry abnormalities

	Parameter (unit)	ERR	TELVC LIMITS	To be presented
Chemistry	Creatinine (µmol/L)	>=1.5 x baseline >=2 x baseline		>=1.5 x baseline >=2 x baseline
	Sodium (mmol/L)	<= 120 >= 150	>= 10 decrease/increase	<= 120 <= 120 AND >= 10 decrease >= 150 >= 150 AND >= 10 increase
	Potassium (mmol/L)	<= 3.5 >= 6	>= 0.5 decrease/increase	<= 3.5 <= 3.5 AND >= 0.5 decrease >= 6 >= 6 AND >= 0.5 increase
	CK (µkat/l)	>=5 x ULN >=10 x ULN		>=5 x ULN >=10 x ULN
	Calcium (mmol/L)	<= 2.0 >= 3.0	>= 0.5 decrease/increase	<= 2.0 <= 2.0 AND >= 0.5 decrease

				>= 3.0 >= 3.0 AND >= 0.5 increase
	Albumin (g/L)	<= 30 <= 20	>= 10 decrease	<= 30 <= 30 AND >= 10 decrease <= 20 <= 20 AND >= 10 decrease
Haematology	Haemoglobin (g/L)	<= 120 <= 100	>= 20 decrease >= 30 decrease	<= 120 <= 120 AND >= 20 decrease <= 100 <= 100 & >= 30 decrease
	Haematocrit	<= 0.35		
	Leukocyte count	<=2.5 x 10^9 >=15 x 10^9	>=2.0 x 10^9 decrease/increase	<=2.5 x 10^9 <=2.5 x 10^9 AND >=2.0 x 10^9 decrease >=15 x 10^9 >=15 x 10^9 AND >=2.0 x 10^9 increase
	Platelet count	<= 100, <= 150 >= 400	>= 50 decrease >= 100 increase	<= 100 <= 100 & >= 50 decrease <= 150 <= 150 & >= 50 decrease >= 400 >= 400 & >= 100 increase

ERR = extended ref range; TELVC = treatment emergent lab/vital sign change.

4.5.3.2 Presentations

For each scheduled visit, descriptive statistics for all clinical chemistry, haematology parameters, and for coagulation parameters will be presented for observed values and change from baseline.

Shift tables of laboratory parameters will be presented with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline as below:

- A summary of baseline versus maximum observation on treatment in each laboratory parameter by treatment group (shift table)
- A summary of baseline versus minimum observation on treatment in each laboratory parameter by treatment group (shift table)

Treatment emergent haematology and chemistry abnormalities by predefined criteria will be presented using the definition in Section 4.5.3.1.

Box plots for haemoglobin, haematocrit, serum creatinine, and eGFR and change from baseline over time will be presented by each treatment group, for all participants in SS.

Line plots for change in haemoglobin and haematocrit from baseline over time will be presented by each treatment group, for all participants in SS.

Supportive laboratory listings will include observed values and changes from baseline for each individual participant as well as abnormalities.

Key subject information of treatment emergent haematology and chemistry abnormalities will be presented using the definition in 4.5.3.1. For a lab value with a treatment emergent abnormality, all timepoints will be included regardless of normal or abnormal.

4.5.4 Clinical Laboratory, Urinalysis

4.5.4.1 Definitions and Derivations

Urinalysis variables that will be measured are detailed in CSP Table 5.

Treatment emergent urinalysis abnormalities will be defined as Table 6. Treatment emergent abnormalities will be based on assessments after first dose of investigational product up to and including safety follow-up visit.

Table 6 Treatment-emergent urinalysis abnormalities

	Parameter (unit)	ERR	TELVC LIMITS	To be presented
Urinalysis	Glucose, protein (Arbitrary U)	>= + >= ++	>= 1+ increase >= 2+ increase	>= + >= + AND >= 1+ increase >= ++ >= ++ AND >= 1+ increase >= ++ AND >= 2+ increase

ERR = Extended reference range; TELVC = Treatment Emergent Lab/Vital sign Change

4.5.4.2 Presentations

Shift tables (“Negative”, “Trace”, “+”, “++”, “+++”, “++++”) from baseline to maximum on-study results will be produced for urinalysis.

Treatment emergent urinalysis abnormalities by predefined criteria will be presented using the definition in Section 4.5.4.1.

Box plots for urine albumin/creatine and change from baseline over time will be presented by each treatment group, for all participants in SS.

Listings will be provided for all laboratory results including urinalysis.

Key subject information of treatment emergent urinalysis abnormalities will be presented using the definition in Section 4.5.4.1.

4.5.5 Other Laboratory Evaluations

4.5.5.1 Definitions and Derivations

Liver Function Parameters

Participants with elevated post-baseline ALT, AST, or Total Bilirubin will be defined as:

any ALT/AST >= 3xULN; Total Bilirubin >= 2xULN

The number and percentages of these participants will be tabulated.

4.5.5.2 Presentations

Table of maximum ALT and AST versus maximum bilirubin will be presented. A listing of key subject information for subjects with potential Hy's Law will be presented.

Scatter plot of maximum ALT or AST versus maximum total bilirubin - multiples of ULN will be presented.

Outputs for potential Hy's Law will include all assessments including unscheduled visits.

4.5.6 Vital Signs

4.5.6.1 Definitions and Derivations

Treatment emergent vital sign abnormalities will be defined as Table 7. Treatment emergent abnormalities will be based on assessments after first dose of investigational product up to and including safety follow-up visit.

Table 7 Treatment-emergent vital sign abnormalities

	Parameter (unit)	ERR	TELVC LIMITS	To be presented
Vital sign	SBP (mmHg)	<90 <80	>=20 decrease	<90 <90 AND >=20 decrease <80
	DBP (mmHg)	<60	>=10 decrease	<60 <60 AND >=10 decrease
	HR (bpm)	>=110	>=20 increase	>=110 >=110 AND >=20 increase
	Body weight (kg)		> 2 kg increase > 4 kg increase	> 2 kg increase > 4 kg increase

ERR = extended ref range; TELVC = treatment emergent lab/vital sign change.

4.5.6.2 Presentations

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline for each treatment group.

Categories below will be used for shift tables:

- SBP: Low (<= 90 mmHg), Normal (> 90 mmHg and < 140 mmHg), High (>= 140 mmHg)
- DBP: Low (<= 60 mmHg), Normal, (> 60 mmHg and < 90 mmHg), High (>= 90 mmHg)
- HR: Low (< 50 bpm), Normal (>= 50 bpm and <= 100 bpm), High (> 100 bpm)
- Respiratory rate: Low (< 12 bpm), Normal (>= 12 bpm and <= 20 bpm), High (> 20 bpm)
- Body temperature: Low (< 36 °C), Normal (>= 36 °C and <= 37.8 °C), High (> 37.8 °C)

Shift tables of vital sign parameters will be presented with frequencies of post-baseline values compared to baseline as below.

- A summary of baseline versus maximum observation on treatment in each vital sign parameter by treatment group (shift table)
- A summary of baseline versus minimum observation on treatment in each vital sign parameter by treatment group (shift table)

Figures for the pre-dose mean (-/+SD) and change from baseline of BP and HR data will be presented on linear scale by each treatment group, for all participants in the SS. Figures for the mean (-/+SD) and change from baseline of BP and HR data at Week1 and Week 3 will be presented on linear scale by each treatment group, for all participants in the SS.

Treatment emergent vital signs abnormalities by predefined criteria including SBP, DBP, HR, and body weight will be presented using the definition of treatment emergent vital sign abnormalities in Section 4.5.6.1.

Key subject information of treatment emergent abnormalities will be presented using the definition in Section 4.5.6.1. For a vital sign with a treatment emergent abnormality, all timepoints will be included regardless of normal or abnormal.

Figures for individual SBP (mmHg)/DBP (mmHg)/HR (bpm) and change from baseline over time by subject with Hypotension (AEDECOD in ("Hypotension" "Blood pressure decreased" "Blood pressure diastolic decreased" "Blood pressure systolic decreased" “Orthostatic hypotension”)) will be presented on linear scale by each treatment group, for all participants in SS.

Line plots for absolute change in body weight from baseline over time will be presented by each treatment group, for all participants in SS.

Supportive vital sign listings will include observed values and changes from baseline, as well as abnormalities.

4.5.7 Electrocardiogram

4.5.7.1 Definitions and Derivations

ECG parameters include ECG mean heart rate, QRS duration, RR interval, PR interval, QT interval, and QTc interval Fridericia. ECG evaluations are collected according to the CSP SoA and specific parameters are listed in CSP Section 8.3.3 or in the eCRF.

Overall assessment of ECG is defined by categories: “Normal”, “Abnormal, not clinically significant” and “Abnormal, clinically significant”.

4.5.7.2 Presentations

For the interpretation of the ECG findings, a shift table will include the number and percentage of participants in the respective overall evaluation category: normal, abnormal not clinically significant, and abnormal clinically significant, at baseline and last on-study

value. For ECG parameters, results and change from baseline to each post-baseline time point will be summarised for each treatment group.

A by-participant listing will be provided for ECG parameters and ECG findings.

4.5.8 Other Safety Assessments

Information for hypersensitivity/Anaphylaxis and injection site reactions will be collected in RAVE. Tables of hypersensitivity/Anaphylaxis and injection site reactions will be presented, please see Section 4.5.2 above.

Information for body weight will be collected in RAVE. Summary table of body weight will be presented as results and change from baseline to each post-baseline time point and will be summarised for each treatment group including placebo.

5 INTERIM ANALYSIS

An IA will be performed after approximately 50% of participants complete Week 25 (Visit 15) with an option to trigger early initiation of Phase III activities. The IA will assess, but not be limited to PVR, mPAP, 6MWD, KCCQ, NT-proBNP, renin, AZD3427 serum concentration, and safety.

In order to maintain the study blind, the study staff who perform the IA will be separate from those in the study team. No details that could compromise the integrity of the study blind will be passed to the study team.

Charters will be finalized before the IA and provided for detailed roles and responsibilities and analysis plan.

6 ANALYSIS OF DATA FROM CHINA AND ASIA

To support ethnic sensitivity evaluation between China and rest of world, Asia and rest of world, evaluation in efficacy, safety and PK in Chinese and Asia population is planned in this study for exploratory purposes for a subset of tables and figures.

6.1 Definition of China and Asia subset

A subset of analyses will be performed for all participants enrolled at sites in China. All participants enrolled from sites in Asian countries will be also included for subset analyses.

Analysis sets

The definition of the analysis sets will be the same as the global cohort as defined in Section 3.2 with the exception of including only participants from China and Asia subset, respectively.

Analysis sets for China subset analysis include the following:

- China Enrolled Analysis Set
- China Full Analysis Set
- China Safety Analysis Set
- China PK Analysis Set
- China Per Protocol Set

Analysis sets for Asia subset analysis include the following:

- Asia Enrolled Analysis Set
- Asia Full Analysis Set
- Asia Safety Analysis Set
- Asia PK Analysis Set
- Asia Per Protocol Set

The analysis sets used for each outcome will also be the same as defined in the Section 4. All outputs for analysis of data from China and Asia will be included into study CSR appendix.

6.2 Analysis Consideration

All participants from China cohort will be included in the global cohort and Asia subset. China cohort and Asia subset analysis will be performed at the same time as the global cohort.

All endpoints selected to be analysed for the China cohort or Asia subset will be derived in the same way as detailed in Section 4. All statistical analyses will be considered exploratory in the China cohort and Asia subset. Considering limited number of participants in China cohort and Asia subset, only descriptive statistics will be presented. No subgroup analysis or sensitivity analysis will be performed for China cohort or Asia subset. No separate listings of individual participants in the China cohort or Asia subset will be produced.

7 REFERENCES

CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

Green et al 2000

Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-55.

Levey et al 2009

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May;150(9):604-612.

Pocock et al 2012
Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012. 33: 176-182

Olink® Explore 3072
Olink® Explore 3072. A high-throughput protein biomarker discovery platform offering uncompromised data quality. Available at: https://www.olink.com/products-services/explore/
(last accessed on 01 November 2022).
Finkelstein et al 1999
Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med 1999; 18:1341–1354.

Redfors et al 2020
Björn Redfors, John Gregson, Aaron Crowley, Thomas McAndrew, Ori Ben-Yehuda, Gregg W Stone, Stuart J Pocock, The win ratio approach for composite endpoints: practical guidance based on previous experience, European Heart Journal, Volume 41, Issue 46, 7 December 2020, Pages 4391–4399

Little and Rubin et al 2002
Statistical analysis with missing data. Second Edition, New York: John Wiley & Sons 2002.

Dong, G et al 2016

A generalized analytic solution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. Pharmaceutical statistics, 15(5), 430–437. https://doi.org/10.1002/pst.1763

8 APPENDIX

Appendix A Handling missing data

A.1 Handling missing date

Generally, the imputation of dates is used to decide if an observation is treatment emergent for AEs or concomitant medications. The imputed dates should not be used to calculate durations, where the results would be less accurate.

The following are the guidelines used when partial dates are detected in the study:

- For missing AE and concomitant medication start dates, the following is applied:
  - Missing day – impute the 1st of the month unless month is the same as month of the first dose of the study drug then impute first dose date.
  - Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.
  - Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st of January of the same year as the end date.
  - Imputed start date should be no later than the end date.
- If not ongoing, for missing AE and concomitant medication end dates, the following is applied:
  - Missing day – impute the last day of the month unless both the month and year are the same as the last dose date and the primary analysis date cut-off (DCO) date then impute the later date between last dose date and the primary analysis DCO date.
  - Missing day and month – Impute 31st December unless the year is the same as the last dose date and the primary analysis DCO date then impute the later date between last dose date and the primary analysis DCO date.

Completely Missing – before imputing a date, consider whether the AE/medication is still ongoing and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present/ medication is still being taken (i.e., do not impute a date). If the AE/medication has stopped and start date is prior to first dose date, then impute primary analysis DCO date. Or if it started on or after first dose date then impute a date that is after primary analysis DCO date.

A.2 Multiple imputation using for primary and secondary estimands

<Step1> Imputation part

Wash-out (Placebo) multiple imputation (under primary estimand)

The below imputation will be used to impute missing post baseline data after the occurrence of an ICE for the primary estimand.

For wash-out (Placebo) multiple imputation, it assumes the statistical behaviour of participants in 1.1, 5.4, and 30.0 mg AZD3427 treatment groups who discontinue becomes that of placebo-treated participants after the time of dropout.

Assuming a joint distribution exists for the data with arbitrary missing data pattern, the Fully Conditional Specification (FCS) method will be used to impute the missing values based on the regression model using only data from placebo group, baseline with stratification factor, age, and sex will be included as covariates. If convergence issue occurs due to small number of subjects in China and Japan category, stratification factor will be removed from the imputation model.

In this method, using seed as 12345, 100 imputed datasets will be created based on SAS ver. 9.4 PROC MI procedure. FCS REG model statement will be used for continuous endpoints and FCS LOGISTIC model statement will be used for binary endpoints.

MAR Imputation

For post baseline missing endpoints that will be imputed using MAR assumption, the imputation details are described below.

Assuming a joint distribution exists for the data with arbitrary missing data pattern, the Fully Conditional Specification (FCS) method will be used to impute the missing values based on the regression model. The imputation model will include treatment group (placebo, 1.1, 5.4, and 30.0 mg AZD3427 treatment groups), baseline, and Week 25 assessment. Stratification factor, age, and sex will be included as covariates in the model. If convergence issue occurs due to small number of subjects in China and Japan category, stratification factor will be removed from the imputation model. In this method, using seed as 12345, 100 imputed datasets will be created based on SAS ver. 9.4 PROC MI procedure. FCS REG model statement will be used for continuous endpoints and FCS LOGISTIC model statement will be used for binary endpoints.

<Step2>Analysis Part

For each of the 100 Imputed datasets created at Step1, LS mean for treatment difference will be derived from the statistical model for the given endpoint.

<Step3>Combine Part

The estimates from the 100 fitted models will be combined to provide an overall estimate with corresponding confidence intervals and p-value using the SAS procedure PROC MIANALYZE (using Rubin’s rule).

Appendix B Calculations of summary scores of KCCQ

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Appendix C Calculations of confidence interval and p-value of win ratio

The calculation of confidence interval and p-value is based on a generalized analytic solution introduced by Dong.

Distribution of the number of winners

Let X_i (i = 1, 2, ...N_t) be the information (e.g., death, graft loss,...etc) for the i^{th} participant in the treatment group; and Y_j (j = 1, 2,...N_c) be the information for the j^{th} participant in the control group. We define a general form of the kernel function K as $K_{ij} = K(X_i,Y_j)$ as follows.

K_{ij} = 1, if the i^{th} participant in the treatment group won over the j^{th} participant in the control group.
K_{ij} = 0, if the i^{th} participant in the treatment group lost to the j^{th} participant in the control group.
K_{ij} = 0, if the i^{th} participant in the treatment group tie with the j^{th} participant in the control group.

The number of winners (n_t) in the treatment group can be counted as

$$n_t = \sum_{i=1}^{N_t} \sum_{j=1}^{N_C} K(X_i, Y_j).$$

n_t is a U-statistic with the kernel function K. Following Wei & Johnson with a reparameterization of applying the multiplication factor $\frac{N_t N_c}{\sqrt{N_t+N_c}}$to the U-statistic defined in the reference, n_t follows the following asymptotic normal distribution. We use AN to denote an asymptotic normal distribution.

$$n_t \sim AN(\theta_t, \sigma_t^2)$$

Where

$$\theta_t = N_t N_c \theta_k$$
$$\theta_k = E[K(X_i, Y_j)]$$
$$\sigma_t^2 = \frac{1}{N_t}\sigma_1^2 + \frac{1}{N_c}\sigma_2^2$$
$$\sigma_1^2 = \frac{N_t N_c}{(N_c - 1)} \sum_{i=1}^{N_t} \sum_{j=1}^{N_C} \sum_{\substack{j'=1 \\ j' \neq j}}^{N_C} [K(X_i, Y_j) - \theta_k]\,[K(X_i, Y_{j'}) - \theta_k]$$

$$\sigma_2^2 = \frac{N_t N_c}{(N_t - 1)} \sum_{j=1}^{N_C} \sum_{i=1}^{N_t} \sum_{\substack{i'=1 \\ i' \neq i}}^{N_t} [K(X_i, Y_j) - \theta_k] [K(X_{i'}, Y_j) - \theta_k]$$

Under the null hypothesis H_0 of the same treatment effect in the treatment and control groups, $\theta_k = \theta_{K0} = E_{H_0}[K(X_i, Y_j)]$, θ_{K0} can be estimated by

$$\widehat{\theta_{K0}} = \widehat{E_{H_0}}[K(X_i, Y_j) = \frac{n_t + n_c}{2N_t N_c}.$$

Therefore, under the null hypothesis H_0:

$$n_t \sim AN(\theta_t, \widehat{\sigma_{t0}^2})$$

Where

$$\widehat{\sigma_{t0}^2} = \frac{1}{N_t} \widehat{\sigma_{10}^2} + \frac{1}{N_c} \widehat{\sigma_{20}^2}$$

$$\widehat{\sigma_{10}^2} = \frac{N_t N_c}{(N_c - 1)} \sum_{i=1}^{N_t} \sum_{j=1}^{N_C} \sum_{\substack{j'=1 \\ j' \neq j}}^{N_C} [K(X_i, Y_j) - \widehat{\theta_{k0}}] [K(X_i, Y_{j'}) - \widehat{\theta_{k0}}]$$

$$\widehat{\sigma_{20}^2} = \frac{N_t N_c}{(N_t - 1)} \sum_{j=1}^{N_C} \sum_{i=1}^{N_t} \sum_{\substack{i'=1 \\ i' \neq i}}^{N_t} [K(X_i, Y_j) - \widehat{\theta_{k0}}] [K(X_{i'}, Y_j) - \widehat{\theta_{k0}}]$$

Similarly, we can derive the kernel function L to compare the j^{th} participant in the control group with the i^{th} participant in the treatment group, such as $L_{ij} = L(X_i, Y_j) = 1$ if the j^{th} participant in the control group won over the i^{th} participant in the treatment group, otherwise, $L_{ij} = 0$. Then the number of winners in the control group n_c and its asymptotic distribution under H_0 can be derived. $\widehat{\sigma_{c0}^2}$ can be calculated analogously to $\widehat{\sigma_{t0}^2}$, and θ_c can be specified analogously to θ_t.

$$n_c = \sum_{i=1}^{N_t} \sum_{j=1}^{N_C} L(X_i, Y_j)$$

$$n_c \sim AN(\theta_c, \sigma_{c0}^2)$$

The covariance of n_t and n_c can be estimated by

$$\widehat{\sigma_{tc0}} = \frac{1}{N_t}\widehat{\sigma_{tc10}} + \frac{1}{N_c}\widehat{\sigma_{tc20}}$$

$$\widehat{\sigma_{tc10}} = \frac{N_t N_c}{(N_c-1)}\sum_{i=1}^{N_t}\sum_{j=1}^{N_C}\sum_{\substack{j'=1\\ j'\neq j}}^{N_C}[K(X_i,Y_j) - \widehat{\theta_{k0}}]\,[L(X_i,Y_{j'}) - \widehat{\theta_{L0}}]$$

$$\widehat{\sigma_{tc20}} = \frac{N_t N_c}{(N_t-1)}\sum_{j=1}^{N_C}\sum_{i=1}^{N_t}\sum_{\substack{i'=1\\ i'\neq i}}^{N_t}\left[K(X_i,Y_j) - \widehat{\theta_{k0}}\right]\left[L(X_{i'},Y_j) - \widehat{\theta_{L0}}\right]$$

$$\widehat{\theta_{L0}} = \widehat{\theta_{K0}} = \frac{n_t + n_c}{2N_t N_c}$$

Therefore, under the null hypothesis H_0, the asymptotic joint distribution of n_t and n_c is

$$\binom{n_t}{n_c} \sim AN\left(\begin{bmatrix}\theta_t\\ \theta_c\end{bmatrix}, \begin{bmatrix}\widehat{\sigma_{t0}^2} & \widehat{\sigma_{tc0}}\\ \widehat{\sigma_{tc0}} & \widehat{\sigma_{c0}^2}\end{bmatrix}\right).$$

Distribution of the win ratio

From above derivation, the number of winners in the treatment group asymptotically follow a normal distribution, namely $n_t \sim AN(\theta_t, \widehat{\sigma_{t0}^2})$. Following the delta method, the logarithm of n_t is asymptotically normally distributed as

$$\log(n_t) \sim AN(\log(\theta_t), \widehat{\sigma_{t0}^2}/(\widehat{\theta_{t0}})^2),$$

where

$$\widehat{\theta_{t0}} = N_t N_c \widehat{\theta_{K0}} = \frac{n_t + n_c}{2}.$$

Similarly, the asymptotic distribution for $\log(n_c)$ can be derived. The asymptotic joint distribution $\log(n_t)$ and $\log(n_c)$ can be derived as

$$\binom{\log(n_t)}{\log(n_c)} \sim AN\left(\begin{bmatrix}\log(\theta_t)\\ \log(\theta_c)\end{bmatrix}, \begin{bmatrix}\widehat{\sigma_{t0}^2}/(\widehat{\theta_{t0}})^2 & \widehat{\sigma_{tc0}}/(\widehat{\theta_{t0}}\widehat{\theta_{c0}})\\ \widehat{\sigma_{tc0}}/(\widehat{\theta_{t0}}\widehat{\theta_{c0}}) & \widehat{\sigma_{c0}^2}/(\widehat{\theta_{c0}})^2\end{bmatrix}\right),$$

where $\widehat{\theta_{c0}} = N_t N_c \widehat{\theta_{L0}} = \frac{n_t + n_c}{2} = \widehat{\theta_{t0}}$.

Therefore, the logarithm of the win ratio is asymptotically normally distributed as:

$$\log(win\ ratio) \sim AN\left(\log\left(\frac{\theta_{t0}}{\theta_{c0}}\right), \widehat{\sigma_{t0}^2}/(\widehat{\theta_{t0}})^2 + \widehat{\sigma_{c0}^2}/(\widehat{\theta_{c0}})^2 - 2\widehat{\sigma_{tc0}}/(\widehat{\theta_{t0}}\widehat{\theta_{c0}})\right).$$

To simplify the notation, let $\widehat{\theta_0} = \widehat{\theta_{c0}} = \widehat{\theta_{t0}} = \frac{n_t+n_c}{2}$. Then under H_0, log(win ratio) follows the following asymptotic normal distribution:

$$\log(WR) \sim AN\left(0, \widehat{\sigma^2_{\log(WR)}}\right),$$

where

$$\widehat{\sigma^2_{\log(WR)}} = \frac{\widehat{\sigma^2_{t0}} + \widehat{\sigma^2_{c0}} - 2\widehat{\sigma_{tc0}}}{(\widehat{\theta_0})^2}.$$

Based on the distribution, the two-sided p-value to test H_0: log(win ratio)=0 (or WR=1) versus H_1: log(win ratio)≠0 (or WR≠1), where ϕ is the cumulative distribution function of the standard normal distribution:

$$p - value = 2 \times \left[1 - \phi\left(\left|\frac{\log(WR)}{\widehat{\sigma_{log(WR)}}}\right|\right)\right]$$

The (1- σ)100% confidence interval for the win ratio can be calculated as follows, where $Z_{1-\alpha/2}$ denotes the (1-α/2) quantile of standard normal distribution.

$$\left(e^{\log(WR) - Z_{1-\alpha/2}\widehat{\sigma_{log(WR)}}}, e^{\log(WR) + Z_{1-\alpha/2}\widehat{\sigma_{log(WR)}}}\right).$$

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