STATISTICAL ANALYSIS PLAN

Sponsor:	Astra Zeneca	Protocol/CIP Number:	D6580C00003
CIL Project Number:	44158		

Protocol/CIP No. D6580C00003

A randomized, double blind, placebo-controlled, parallel group, multicentre, phase 2a study to assess target engagement, safety and tolerability of AZD4831 in patients with Heart Failure with preserved Ejection Fraction (HFpEF)

Statistical Analysis Plan

Prepared for:
AstraZeneca AB

Version 5.0 Date 12NOV2020

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VERSION HISTORY OF IMPLEMENTED PLANS

Version	Date	Revision Author	Comments
1.0	11APR2019	█	First version
2.0	04JUL2019	███████	- Section 7.1: details added regarding the calculations of geometric mean and CV for percent change from baseline - Sections 6.4.3 and 8.6.3: Endogenous MPO analysis excluded from the SAP as this is considered as an exploratory biomarker and is planned to be analysed separately. - Section 6.4.1: wording updated to stick to laboratory documentation. Spiked sample is replaced by Positive control sample. And zymosan stimulated samples are specified for baseline, Visit 3, Visit 5 and Visit 7. - Section 12: Typos corrected - Sections 6.4.3 and 6.6.3: Table 5 and Table 7 updated with AZ standard SI units.
3.0	17DEC2019	██████	- Section 5.2: timing of the interim analysis is clarified. A maximum of 37 patients will be randomized and the last patient should be treated for approximately 30 days. - Section 5.2: Safety Review Committee and Data Review Committee Charter section 9.1 was updated and the associated bullet is deleted in this section. - Section 6.2.2: updated wording for the visits. - Section 7.1: atrial fibrillation is considered at the time of randomization in IVRS and not within 12 months prior to or at randomization.

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			- Section 7.4.1: Two cut-off dates are considered at the time of interim analysis as described in the SRC/DRC charter v3.0.
4.0	13FEB2020	▮▮▮▮▮	- Section 2, Section 4.1, Section 4.4, Section 4.5: SAP updated to be consistent with protocol v4.0.
5.0	12NOV2020	▮▮▮▮▮	- Signature page: GPS role updated. - Section 6.2: Blood sampling added in the footnote as it is done pre dose as per CSP. - Section 6.4.2: CFVR valid measurements defined as per external vendor data. - Section 6.4.3: echocardiography measurements defined as per external vendor data. All available cfPWV/bPWA measurements will be included in the analysis even if there is only one measurement. Table 5: update of NT-proBNP unit - Section 6.4.4: KCCQ physical limitation score will be of interest as well as per corresponding endpoint. - Section 6.6.4: Sentence about LoQ deleted as not applicable for vital signs. - Section 8.1: COVID-19 listing added - Section 8.3.3: PK population title replaced by PK analysis set for consistency. - Section 8.6.3: *Details added about echocardiography parameters (at rest/at hyperaemia). Normality distribution is considered for GLS and right ventricular free wall longitudinal strain as these parameters are negative results. * ANCOVA to be used instead of MMRM for echocardiography parameters measured at hyperaemia.

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			* KCCQ physical limitation score will be analysed to address the corresponding endpoint.
			- Table of contents:
			   *Table 14.1.11: title updated
			   *Tables/figures updated according to updates done in section 8.6.3.
			   *typos corrected.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

6MWT	6 Minutes Walking Test
AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ANCOVA	Analysis of Covariance
AF	Atrial Fibrillation
ATC	American Thoracic Chemical
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
BILI	Total Bilirubin
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
bPWA	Brachial Pulse Wave Analysis
cfPWV	Carotid-femoral Pulse Wave Velocity
CFVR	Coronary Flow Velocity Reserve
CI	Confidence Interval
CK	Creatine Kinase
CM	Concomitant Medication
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DRC	Data Review Committee
ECG	Electrocardiogram
E/e'	Diastolic Function (measured as ratio between early mitral inflow velocity and mitral annular early diastolic velocity)
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EndoPAT	Endothelial Function Measurement
EOS	End of Study
EOT	End of Treatment
FSH	Follicle-stimulating Hormone
GeoMean	Geometric Mean
GLS	Global Longitudinal Strain
Hb	Haemoglobin
HbA1C	Glycosylated Haemoglobin, Type A1C
HBsAg	Hepatitis B Surface Antigen
HDL	High-Density Lipoprotein
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HLR	High Level Result
hsCRP	High Sensitivity C-reactive Protein
hsTnT	High-sensitive Troponin T
ICF	Informed Consent Form
IDRP	Integrated Data Review Plan
IP	Investigational Product

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IPD	Important Protocol Deviations
IVRS	Interactive Voice Response System
IxRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAD	Left Anterior Descending
LAVI	Left Atrium Volume Index
LDL	Low-Density Lipoprotein
LH	Luteinizing Hormone
LoQ	Limit of Quantification
LSMeans	Least-Squares Means
LVM	Left Ventricular Mass
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MoP	Manual of Procedures
MPO	Myeloperoxidase
NT-proBNP	N-terminal pro b-type Natriuretic Peptide
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred Term
PR	Pulse Rate
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
REML	Restricted Maximum Likelihood
RHI	Reactive Hyperemic Index
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedures
SP (POW)	Spatial Power Covariance Structures
SRC	Safety Review Committee
T3	Triiodothyronine
T4	Thyroxine
TC	Telephone Contact
TDE	Transthoracic Doppler Echocardiography
TE	Target Engagement
TG	Triglycerides
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UN	Unknown Day
UNK	Unknown Month
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
WHO	World Health Organisation

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2. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol version 4.0 dated 9 JAN 2020. The SAP includes detailed procedures for executing the interim and final statistical analyses related to the primary, secondary, safety and explorative objectives of the study, with the exception of:

- Effect of AZD4831 on MPO-related biomarkers compared to placebo
- Potential future exploratory research aimed at exploring biomarkers involved in Pharmacokinetics (PK), Pharmacodynamics (PD), efficacy, safety and tolerability related to heart failure with preserved ejection fraction (HFpEF) and AZD4831 treatment,
- All secondary and exploratory objectives in patients with elevated Myeloperoxidase (MPO)-pathway biomarkers, and
- Potential future exploratory genetic research

The SAP is finalized and signed prior to the conduct of the interim analysis. If needed, revisions to the approved SAP may be made prior to database hard lock in a SAP amendment.

3. STUDY OBJECTIVES

The primary objective is:

Primary Objective:	Endpoint/Variable:
To compare the effect of AZD4831 to placebo on target engagement (TE)	Change from baseline in target engagement marker, defined as ex vivo zymosan stimulated MPO specific activity (MPO activity divided by MPO protein mass), normalised. Hereafter referred as TE biomarker throughout the rest of the document.

The secondary objectives are:

Secondary Objective:	Endpoint/Variable:
To compare the effect of AZD4831 to placebo on coronary flow velocity reserve (CFVR)	Change from baseline in CFVR measured in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by transthoracic Doppler echocardiography (TDE)
To compare the effect of AZD4831 to placebo on 6 minutes walking test (6MWT)	Change from baseline in Walking distance
To assess the PK of AZD4831 after repeated dosing	Standard model population PK parameters to be reported in a separate report

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The safety objective is:

Safety Objective:	Endpoint/Variable:
To assess safety and tolerability of AZD4831	- Adverse events/Serious adverse events (AEs/SAEs) including incidence of maculopapular rash grade 3 - Vital Signs - Clinical chemistry/haematology/urinalysis parameters - Electrocardiogram (ECG) assessments

The explorative objectives are:

Exploratory:	Endpoint/Variable:
To explore the effect of AZD4831 on myocardial strain, measured as global longitudinal strain (GLS) compared to placebo	Change from baseline in GLS as measured by strain imaging echocardiography
To explore the effect of AZD4831 on right ventricular free wall longitudinal strain compared to placebo	Change from baseline in right ventricular free wall longitudinal strain measured by strain imaging echocardiography
To explore the effect of AZD4831 on left atrium reservoir strain compared to placebo	Change from baseline in left atrium reservoir strain measured by strain imaging echocardiography
To explore the effect of AZD4831 on diastolic function (measured as ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e')) compared to placebo	Change from baseline in E/e' as measured by standard echocardiography
To explore the effect of AZD4831 on peripheral endothelial function compared to placebo	Change from baseline in reactive hyperemic index (RHI)
To explore the effect of AZD4831 on pulse wave velocity (PWV) and pulse wave analysis (PWA) compared to placebo	Change from baseline in PWV and PWA
To explore the effect of AZD4831 on N-terminal pro b-type Natriuretic Peptide (NT-proBNP) compared to placebo	Change from baseline in NT-proBNP values
To explore the effect of AZD4831 on changes in health-related quality of life (QoL) compared to placebo	Change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, with specific focus on physical function domain
To explore the effect of AZD4831 on left atrium volume index (LAVI) compared to placebo	Change from baseline in LAVI

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Exploratory:	Endpoint/Variable:
To explore the effect of AZD4831 on MPO-related biomarkers compared to placebo*	Change from baseline in MPO- related biomarkers
To collect and store samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, efficacy, safety and tolerability related to HFpEF and AZD4831 treatment*	Exploratory biomarker analysis in plasma, serum and urine
To explore all secondary and exploratory objectives in patients with elevated MPO-pathway biomarkers*	Corresponding variables for secondary and exploratory endpoints
Optional: To collect and store samples for potential future exploratory genetic research aimed at e.g. identifying/exploring genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD4831 treatment*	

* These objectives are out of this SAP scope.

4.   STUDY DESIGN

4.1.   General Design

A summary of the study will be presented here, full details are provided in the clinical study protocol (CSP) Section 4.

This is a randomized, double blind, placebo controlled study including approximately 96 randomized patients with HFpEF. Patients with heart failure with mid-range ejection fraction (HFmrEF) will also be included in the study and will hereafter be included in the definition of HFpEF, if not otherwise specified. The study will be conducted at approximately 10 sites and 5 countries. All patients will be treated once daily with AZD4831 or placebo for approximately 90 days. The study will be divided into two parts, Part A and Part B. In part A 37 patients will be randomized and treated for approximately 90 days. An interim analysis will take place when all patients in part A have been treated for approximately 30 days. The safety, tolerability and target engagement will be evaluated in the interim analysis and after the evaluation the randomization to Part B may proceed. In part B the approximate 59 remaining patients will be randomized and treated for approximately 90 days.

Part A:

At visit 1 the patients will be checked for eligibility and enrolled to the study. 37 patients will be randomized at visit 2 in a 2:1 ratio to once daily dosing of AZD4831 or matching

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placebo. The patients will be dosed the first 10 days (until visit 3) with a starting dose of ▉ ▉ once daily AZD4831 or matching placebo. After 10 days, at visit 3, the dose will be increased to ▉ AZD4831 or matching placebo and patients will be treated for another 20 days (visit 4 and visit 5). When all patients have been treated for approximately 30 days an interim analysis will follow but the patients included in part A will continue the treatment at ▉ AZD4831 or matching placebo once daily for another 60 days until stop of treatment and complete the next visit approximately every 30 days for visit 6 and visit 7. After the stop of treatment patients will be followed-up (visit 8) after approximately 30 days.

After evaluation of the interim analysis patients may be randomized to Part B of the study, see section 9.5 of the CSP for information regarding the interim analysis.

Part B:

At visit 1 patients will be checked for eligibility and enrolled into study. Approximately, 59 patients will be randomized at visit 2 in a 2:1 ratio to once daily dosing of AZD4831 or matching placebo. Patients in part B will be dosed the first 10 days (until visit 3) with a starting dose of ▉ AZD4831 or matching placebo once daily. At Visit 3, further level of dosing for all patients will depend on the Interim Analysis results (it can be ▉ ▉ once daily depending on safety profile and target engagement). Treatment will continue for approximately 80 days more to achieve 90 days in total in Part B. Following visit 3 patients will complete the next visit 20 days (visit 4), 30 days (visit 5), 60 days (visit 6) and 90 days (visit 7) after randomization. After the stop of treatment patients will be followed-up (visit 8) for approximately 30 days.

Figure 1: Study design

Part A: 37 randomized patients
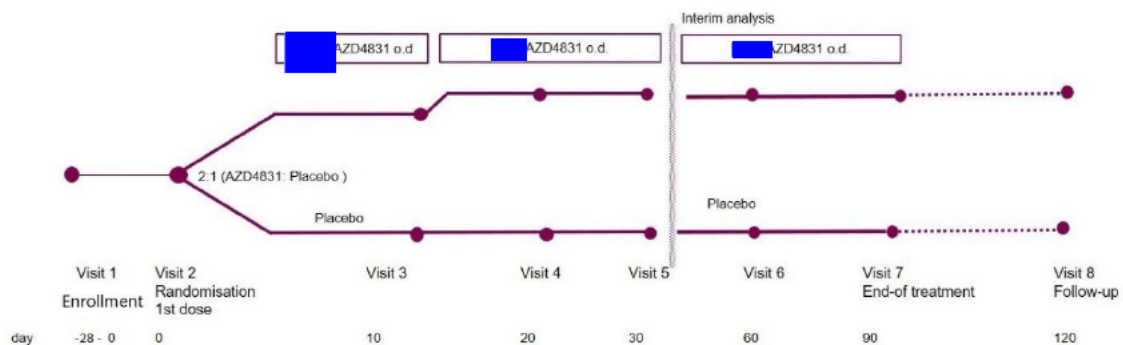
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Part B: Approximately 59 randomized patients
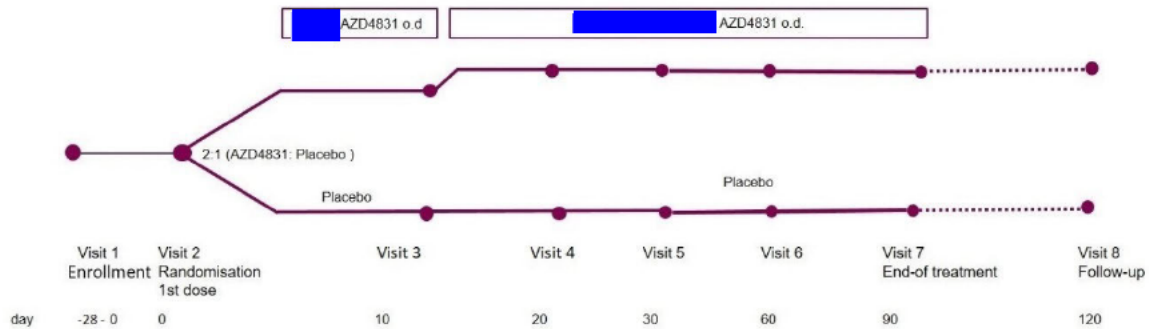
4.2. Discussion of Study Design

A randomized, blinded, parallel-group, multicentre, placebo-controlled study design is standard in Proof-of-Principle studies and is considered the best design to achieve the objectives of the study, from both safety and efficacy perspectives. Full details regarding the rationale for study design, doses and control groups are reported in Section 4 of the CSP.

4.3. Method of Assignment of Patients to Treatment Groups

All patients will be centrally assigned to randomized investigational product (IP) using an interactive voice/web response system (IxRS). Randomization to IP will be performed in balanced blocks to ensure approximate balance between the treatment groups (2:1).

The randomization will be stratified by atrial fibrillation (AF) (Yes vs No).

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

4.4. Blinding

All patients will be blinded with respect to active or placebo treatment, but not the dose that is selected for the active treatment after the interim analysis.

The randomization codes will be computer generated and loaded into the IxRS database. The IxRS will provide to the investigator or pharmacist the kit identification number to be allocated to the patient at the dispensing visit. At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient.

The IxRS will be programmed with blind-breaking instructions. The randomization code should not be broken except in medical emergencies when the appropriate management of

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the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca within 24 hours after breaking the blind, without revealing the treatment given to the patient to the AstraZeneca staff. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The randomization list should be sent to the personnel analyzing the PK samples.

In addition, all personnel involved with the analysis of the study will remain blinded until database lock and CSP deviations identified. The only exception are study independent personnel who are involved in the interim analyses (Please refer to Section 7.4 of the CSP).

4.5. Determination of Sample Size

The study has been powered to show a statistically significant result for the primary endpoint, and first secondary endpoint. To preserve the overall type1-error at 5% when testing these two endpoints a closed test procedure will be used where the first secondary endpoint will be tested only if the primary endpoint is significant. That is, the primary endpoint will be tested at 5% significant level and if the test is positive the first secondary endpoint will also be tested on a significant level of 5%. If the primary objective is not significant the first secondary objective will also be declared non-significant.

In addition, to get information about incidence rate of generalised maculopapular rash Grade 3 in the AZD4831 arm a randomization allocation ratio of 2:1 (active versus placebo) will be used. With approximately 96 randomized patients, this will give at most 64 patients on active drug for rash evaluation and about 53 patients on AZD4831 versus 27 patients on placebo for evaluation of the first primary endpoint and the first secondary endpoint. It has been deemed that about 64 patients provide sufficient information about the incidence rate of rash when treated with AZD4831.

A relative change in TE biomarker to end of treatment comparing AZD4831 to placebo is assumed to be log-normal distributed with a coefficient of variation (CV) of 60% (based on data from the multiple ascending dose (MAD) study). An expected reduction of 15% from baseline to end of treatment in TE biomarker in placebo, and an expected reduction of 50% from baseline to end of treatment in TE biomarker in AZD4831 are assumed (based on data from the MAD study, Baldus et al 2006). A fold change of at least 1.7 in TE biomarker comparing AZD4831 to placebo will give more than 95% power for a two-sided test on a 5% significant level with 53 patients on AZD4831 versus 27 patients on placebo, accounting for patient drop out. If the dose level is adjusted after the interim analysis the power will still

be at least 90% for testing the primary endpoint hypothesis with the assumption of 25 patients on AZD4831 and 25 patients on placebo.

Assuming a log-normal distribution of the CFVR and an expected 20% increase in CFVR in the AZD4831 group compared to placebo with a CV of 30%, 53 versus 27 patients in the treatment group and placebo respectively is required to achieve 80% power with a one-sided confidence interval (CI) of 95%.

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1. Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this SAP.

5.2. Changes from the Analyses Planned in the Protocol

- In CSP and SAP Table 2 and Figure 1 (as per CSP), Day from randomization and from first study drug intake is called Day 0. However, in the rest of the SAP and in all the statistical outputs Day 1 as described further down will be used instead.
- CSP Section 6.5 states that concomitant medications (CMs) are those that patient is receiving at the time of enrolment or receives during the study. However, for the purpose of the statistical analysis, the definition is updated so that there is no overlap with prior medications. See section 8.5.
- CSP Section 9.7 refers to the number of patients who discontinue the study due to generalised maculopapular rash Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher. However, there is no higher grading than 3 for generalised maculopapular rash.
- CSP section 1.2 states that when all 37 patients have been treated for approximately 30 days an interim analysis will follow. This should be understood as at the time of interim analysis, 37 patients will be randomized and the last patient treated for approximately 30 days. It may be that patients discontinue before 30 days of treatment. Thus, the number of patients treated for approximately 30 days may be less than 37 patients at the time of interim analysis.
- CSP section 9.5 states that the interim analysis plan will describe the analysis performed at the interim analysis but there is no document named interim analysis plan. Both SAP and Safety Review Committee (SRC) and Data Review Committee (DRC) Charter describe the interim analysis.

6. BASELINE, EFFICACY and Safety EVALUATIONS

6.1. Schedule of Evaluations

The assessments to be conducted at each analysis visit are displayed in the following table.

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Table 2: Study of Assessments

	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	Enrollment	Randomization ▇▇▇	▇▇ – Part A ▇▇▇▇▇ - ▇▇ – Part B								End of Treatment	Follow-up
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		Within 28 days from enrollment	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
Informed consent	X											
Informed consent for Genetic sampling (optional)	X											
Inclusion /exclusion criteria	X	X										
Alcohol, Drug of abuse and nicotine use	X											
Demography	X											
Medical & Surgical history	X											

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	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	**Enrollment**	**Randomization**	– Part A – Part B								**End of Treatment**	**Follow-up**
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		**Within 28 days from enrollment**	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
Pregnancy test (serum or urine, females only)	X											
Randomization		X										
IP dispensed		X	X				X					
IP returned and accountability checked			X				X	.			X	
IP intake at site		X	X	X	X[c]	X	X		X[c]	X		
Patient Diary Card hand out		X										
Patient Diary Card review by site staff			X	X		X	X	X		X	X	

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	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	Enrollment	Randomization ▇	▇ – Part A / ▇ – Part B								End of Treatment	Follow-up
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		Within 28 days from enrollment	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
Optional Genetic Sampling		X										
Physical examination[d]	X	X	X	X			X	X			X	X
Supine blood pressure (BP) and pulse rate (PR)	X	X	X	X		X	X	X		X	X	X
Height	X											
Weight	X	X	X	X		X	X	X		X	X	
Body temperature	X	X		X		X	X	X		X	X	
Digital 12 lead ECG	X	X	X	X			X	X			X	X
CM	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X

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	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	**Enrollment**	**Randomization** ▆▆▆	▆▆ – Part A ▆▆▆▆▆ – Part B								**End of Treatment**	**Follow-up**
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		**Within 28 days from enrollment**	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
Safety laboratory assessment	X[j]	X	X	X[f]		X[f]	X	X[f]		X[f]	X	X
Serology	X											
PK sampling for AZD4831			X (pre-dose only)	X (pre-dose only)		X (pre-dose only)	X (pre-dose only)	X (pre-dose only)		X (pre-dose only)	X[g]	X
TE biomarker		X	X				X				X	
NT-ProBNP/BNP	X[h,j]	X					X				X	
Blood sampling for Lipid status		X					X				X	

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	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	Enrollment	Randomization ▆▆▆▆	▆▆▆ – Part A ▆▆▆▆▆▆▆ – Part B								End of Treatment	Follow-up
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		Within 28 days from enrollment	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
Other laboratory samples		X					X				X	
Collection of exploratory samples		X		X		X	X	X		X	X	X
Endogenous MPO mass activity measurement		X					X				X	
CFVR measurement		X									X	
Echocardiography	X[i]	X					X				X	
EndoPAT™ test		X					X				X	
PWV/PWA		X					X				X	

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	Visit 1[a,j]	Visit 2[a,j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8
Description	Enrollment	Randomization ▮▮▮	▮▮ – Part A ▮▮▮▮▮ – Part B								End of Treatment	Follow-up
Day from randomization	-28 to 0	0	10	20	20	20	30	60	60	60	90	120
Visit window (in relation to randomization)		Within 28 days from enrollment	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/-4 days	+/-4 days	+/-4 days	+2 days or – 7 days	+/-4 days
6MWT		X					X				X	
KCCQ		X					X				X	X
Patient arrives fasting to visit		X					X				X	

[a] Visit 1 and visit 2 may be performed on the same day if deemed operationally feasible by site. If so, laboratory sampling for inclusion/exclusion criteria at visit 1 will be analysed locally. Laboratory sampling from visit 2 will be analysed centrally. Other assessments that co-occur at visit 1 and 2 need to be performed only once and recorded in the eCRF according to Completion Guidelines.

[b] Visit 4 and/or visit 6 may be performed as a home visit if operationally feasible in part A and part B. After interim analysis AstraZeneca may decide to make visit 4 and/or visit 6 in part B to a visit that could optionally be performed as a telephone contact (TC) with the patient, if judged appropriate by investigator.

[c] If home visit, patient should be instructed not to take the morning dose on the same day as visit.

[d] At visit 1, visit 4 and visit 8 a complete physical examination is performed. At all other visits a brief physical examination will be performed, see section 8.2.2 of the CSP. In case visit 1 and visit 2 occur on the same day, the full physical examination should be performed.

[e] AEs to be collected from first dose until completion of visit 8, SAEs to be collected from signing of informed consent form (ICF) until completion of visit 8.

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^f   A modified safety sample panel will be taken at visit 4 and visit 6, see Table 6 in CSP.

^g   At visit 7 PK is taken at predose, 0.5 -1h, 1-3h and >3h after dose, there should be at least 1 hour between the post-dose sampling occasions. At the other visits PK is only to be taken predose.

^h   For inclusion at visit 1 NT-proBNP or BNP can be used. For all other visits NT-proBNP should be analysed centrally.

ⁱ If echocardiography data is available in medical records from within 1 year before enrollment it may be used for inclusion/exclusion. If not available a simplified echo screen protocol needs to be performed at visit 1 focusing on ejection fraction (EF), LAVI, E/e', left ventricular mass (LVM) and image analysis will be performed by local echo lab. In case visit 1 and 2 occur on the same day the simplified echo screen will be performed first to judge if patient is eligible, thereafter the full echo screen protocol for visit 2 should follow

^j Subjects may enter a screening period up to 28 days prior to visit 2. If visit 1 is performed more than 14 days prior to visit 2, all assessments except blood and urine sampling should be completed at that visit. Blood and urine samples related to visit 1 must be taken within 14 to 0 days prior to visit 2 to ensure patient eligibility

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6.2. Time Point Algorithms

6.2.1. Relative Day

The date of first dose of IP will be considered relative day 1, and the day before the first dose of IP will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the first dose of IP:

Date of Assessment – Date of First Dose of IP + 1.

For days before the first dose of IP:

Date of Assessment – Date of First Dose of IP.

6.2.2. Windows

For the purpose of statistical analysis, the visit numbers will be recalculated in terms of study days since the first day of the trial medication, as illustrated in the following table:

Table 3: Analysis Windows

Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
Visit 1 (Screening)	-28 to 1	-28 to 1
Visit 2 (Randomization)	1	1
Visit 3	10	6 to min (14, last dose) [a, b]
Visit 4	20	16 to min (24, last dose) [a, c]
Visit 5	30	24 to min (36, last dose) [a, d]
Visit 6	60	52 to min (68, last dose) [a, e]
Visit 7 End of treatment (EOT)	90	76 to min (105, last dose) [a, f]
Visit 8 End of study (EOS)	120	>= last dose + 26 days [a]

[a] Last dose date of study drug may be imputed.

[b] Only if the day of last dose of IP ≥ 6

[c] Only if the day of last dose of IP ≥ 16

[d] Only if the day of last dose of IP ≥ 24

[e] Only if the day of last dose of IP ≥ 52

[f] Only if the day of last dose of IP ≥ 76

Measurements collected outside of the above analysis visit windows will be labelled as "Unscheduled visit" and numbered as the previous analysis visit together with the number of the unscheduled visit. So, for instance, the first visit occurring after Visit 4 but outside of the visit window will be numbered 4.1.

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For all assessments the following rules will apply:

- If a patient has more than 1 assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used.
- If several measurements are collected within the same distance from the scheduled study day, the data of the latest visit after the scheduled study day within that window will be used.
- If several measurements are collected on the same window and study day, the average value (for numeric values)/worst (i.e. max) value which has been observed during a study period (for categorical values) will be used. (Note that for ECGs collected on the same day if there is a tie in the overall ECG evaluation results, the worst clinically significant value will be used for the analysis). For numeric values, the analysed value will be the arithmetic mean for normal distributed variables and the geometric mean for log-normal distributed variables.

6.2.3. Phases

For the analysis of some safety variables (including AEs and urinalysis), analysis phases will be defined in terms of study days from first day of the study medication, as illustrated in the following table:

Table 4: Analysis phases

Phase	Phase Window for Analysis (Days)
Baseline phase	before first dose of study IP (day <1[a])
On-treatment phase	From day 1[b] to $\leq$ 14 days after last dose of study drug[c]
Off-treatment phase	>14 days after last dose of study drug[c]

[a] Includes all measurements collected prior to the first dose of IP (defined by the start date and start time of first IP intake). First dose date of IP may be imputed. If the measurement is collected on the day of first dose of IP, and the time of collection cannot determine if the measurement was before or after study drug intake, then two cases should be considered:

- if time is not collected and the measurement is done before first dosing as per protocol (physical examination, vital signs, KCCQ, ECG, PVW/PWA, EndoPAT, echocardiography, CFVR, 6MWT, blood sampling), the measurement will be considered as pre dose.
- in all other cases, the measurement will be considered after study drug intake.

[b] Includes all measurements collected on the day of first dose of IP (Day 1), at the time of IP intake and after.
[c] Last dose date of study drug may be imputed.

6.3. Baseline Assessments

Baseline measurement is defined as last measurement obtained prior to first IP intake.

The following baseline assessments will be conducted prior to initial IP administration:

- Medical and procedure history

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- Alcohol, drug of abuse and nicotine use
- Demographics (date of birth, gender, ethnicity, race, country code)
- Physical examination
- CM
- Vital signs (Supine BP, PR, height, weight and body temperature)
- Safety laboratory assessments
- ECG
- Efficacy assessments (echocardiography, CFVR, PWV/PWA, EndoPAT (RHI), 6MWT (cumulative walking distance), laboratory assessments)
- KCCQ

6.4. Efficacy Variables

6.4.1. Primary Efficacy Variable(s)

The primary efficacy variable (TE biomarker) will be calculated as described below:

1   The ratio of MPO activity (ng/mL) over MPO protein mass (ng/mL) is calculated at each timepoint (baseline, Visit 3, Visit 5, Visit 7) for each individual for zymosan stimulated samples.

2   The ratio is then normalized by subtracting the individual positive control which is computed as the ratio of MPO activity (ng/mL) over MPO protein mass (ng/mL) from the positive control sample collected pre-dose (baseline).

Unless otherwise specified, values below the lower limit of quantification (LoQ) will be set at $LoQ/(sqrt(2))$.

6.4.2. Secondary Efficacy Variables

Unless otherwise specified, values below the lower limit of quantification (LoQ) will be set at $LoQ/(sqrt(2))$.

CFVR measurement

CFVR is measured in the LAD coronary artery before, and during constant adenosine infusion at a rate of 140µg/kg/min for 10 minutes using conventional colour Doppler ultrasound equipped with coronary imaging protocol. For details see manual of procedures (MoP).

For the CFVR, only valid measurements will be used for the analysis.

6MWT

The 6MWT will be conducted based on the American Thoracic Society (ATS) Guidelines. 6MWT is defined as the distance in meters walked by the patient during a six-minute period. For detailed description of the 6MWT procedures please refer to MoP. The cumulative walking distance (meters) will be collected at each visit as indicated in Table 2.

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PK

Refer to Section 6.5.

6.4.3. Exploratory Efficacy Variables

Unless otherwise specified, values below the lower limit of quantification (LoQ) will be set at $LoQ/(sqrt(2))$.

Echocardiography (GLS, right ventricular free wall longitudinal strain, left atrium reservoir strain, LAVI and E/e')

Comprehensive echocardiographic examination will be performed with patients in the left recumbent position at rest. Standard clinical cardiac transducers will be used for B-mode, colour Doppler, and tissue Doppler imaging. For detailed description please refer to MoP.

Only valid measurements will be analysed.

cfPWV and bPWA

cfPWV is measured in a single step with a simultaneous measurement by femoral cuff and carotid placed tonometer. bPWA is conducted with a brachial cuff recording. For details see MoP.

The following variables from cfPWV/bPWA will be collected/derived at the times presented in the study assessments schedule, section 6.1:

- Augmentation index (%),
- Carotid-femoral pulse wave velocity (ms),
- Pulse pressure amplification (ratio) - derived variable,
- Central pulse pressure (mmHg),
- Central blood pressure systolic (mmHg),
- Central blood pressure diastolic (mmHg),
- Brachial blood pressure systolic (mmHg),
- Brachial blood pressure diastolic (mmHg).

Two PWA measurements and two PWV measurements per scheduled measurement time point will be required and each measurement must meet all predefined quality control criteria defined in the SphygmoCor study manual (referred hereafter as "acceptable" measurements). If any measurement fails to meet any of the quality control criteria, additional measurements must be performed until two measurements of acceptable quality are obtained.

For the purpose of the analysis, only data from subjects with acceptable measurements will be used.

In addition, the average per visit for cfPWV/bPWA parameters will be calculated as follows and used for the summaries and analysis:

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- If two or more acceptable measurements are reported, the average of all the values will be used.
- If only one acceptable measurement is reported, it will be displayed for the average.
- If all measurements are missing, then the average will be missing

Pulse pressure amplification is a derived variable and will be calculated as:

(Brachial blood pressure systolic – Brachial blood pressure diastolic)/(Central blood pressure systolic – Central blood pressure diastolic).

Note that central blood pressure systolic cannot physiologically equal central blood pressure diastolic; thus, the denominator cannot equal 0. If one of the values used for calculating pulse pressure amplification is missing, then pulse pressure amplification will be missing.

The exploratory endpoints concerning cfPWV/bPWA are the change at visit 5 and EOT from baseline. Baseline value is defined as in section 6.3.

Endothelial function measurement -EndoPAT™ (RHI)

The endothelial function measurement by peripheral arterial tonometry (EndoPAT™) will be conducted based on instructions provided by the EndoPAT™ device distributor (Itamar Medical Ltd., Caesarea, Israel). For detailed description of the EndoPAT™ measurement procedures measurement please refer to MoP.

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Laboratory assessments

Blood samples will be collected at the visits indicated in Table 2 for the following assessments:

Table 5: Laboratory assessments (SI units)

Laboratory Assessments	Parameter
Efficacy laboratory assessments	TE Biomarker
	BNP or NT-proBNP* (pmol/L)
Lipid status assessments	Cholesterol (mmol/L)
	Low-density lipoprotein (LDL) (mmol/L)
	High-density lipoprotein (HDL) (mmol/L)
	Triglycerides (TG) (mmol/L)
	Apolipoprotein A1 (ApoA1) (g/L)
	Apolipoprotein B (ApoB) (g/L)
Other laboratory assessments	Cystatin-C (mg/L)
	High-sensitive Troponin T (hsTnT) (ng/mL)
	Glycosylated Hemoglobin, Type A1C (HbA1c) (%)
	Blood urea nitrogen (mmol/L)
	Insulin (pmol/L)
	Exploratory Biomarkers
	Endogenous MPO

*Only NT-proBNP central labs will be used for the statistical summaries/analyses.

Mandatory collection of samples for endogenous MPO activity and other exploratory biomarker research is also part of this study but will be analysed separately. Plasma/serum/urine samples for exploratory analysis of biomarkers that may be related to PK, metabolites, PD, efficacy, response to treatment or safety and tolerability of AZD4831 or related to HFpEF will be collected from all patients as specified in Table 2.

6.4.4. Patient Reported Outcome Questionnaire

The KCCQ is a psychometrically validated questionnaire developed for patients with congestive heart failure (Green et al 2000). It is a 23-item, self-administered health status measure that quantifies physical limitations, symptoms, social interference, self-efficacy and quality of life. Results for each domain are summarized and transformed to a score of 0 to 100; higher scores indicate better health status. To summarize the multiple domains of health status quantified by KCCQ, an overall summary score (KCCQ-os) has been developed that includes the physical limitation, symptoms, quality of life and social interference domains of KCCQ. The KCCQ English US Master version is enclosed in Appendix G of the CSP.

KCCQ will be answered by patients on paper at visits as outlined in Table 2.

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Table 6: KCCQ Summary Scores

Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
1 / Physical Limitations	Q1a= Dressing Yourself Q1b= Showering Bathing Q1c= Walking 1 block on level ground Q1d=Doing Yardwork, Housework, Carry Grocery Q1e=Climbing a Flight of Stairs Without Stop Q1f=Hurrying or Jogging	- Extremely Limited=1 - Quite a Bit Limited=2 - Moderately Limited=3 - Slightly Limited=4 - Not at All Limited=5 - Limited for Other Reason or Did Not Do the Activity=missing value	If at least three of Questions 1a-1f are not missing, then Physical Limitation Score is calculated as below: **Physical Limitation Score = 100*[(mean of Questions Q1a-Q1f actually answered) – 1]/4**
2 / Symptom Stability	Q2=Change in heart failure symptoms	- Much Worse=1 - Slightly Worse=2 - Not Changed=3 - Slightly Better=4 - Much Better=5 - I've had No Symptoms Over The Last 2 Weeks=3	If Question 2 is not missing, then Symptom Stability Score is calculated as below: **Symptom Stability Score = 100*[(Question 2) – 1]/4**
3 / Symptom Frequency	Q3=Have Swelling in Feet/Ankles/Legs	- Every morning = 1 - 3 or more times a week but not every day = 2 - 1-2 times a week = 3 - Less than once a week = 4 - Never over the past 2 weeks = 5	If at least two questions Q3, Q5, Q7 and Q9 are not missing, then: $S3 = [(Q3\ response) – 1]/4$ $S5 = [(Q5\ response) – 1]/6$

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
5 / Symptom Frequency	Q5=Times Fatigue Limited Ability	- All of the time = 1 - Several times a day = 2 - At least once a day = 3 - 3 or more times a week but not every day = 4 - 1-2 times a week = 5 - Less than once a week = 6 - Never over the past 2 weeks = 7	$S7 = [(Q7\ response) - 1]/6$ $S9 = [(Q9\ response) - 1]/4$ and Symptom Frequency Score is calculated as below: **Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)**
7 / Symptom Frequency	Q7=Times Shortness of Breath Limit Ability	- All of the time = 1 - Several times a day = 2 - At least once a day = 3 - 3 or more times a week but not every day = 4 - 1-2 times a week = 5 - Less than once a week = 6 - Never over the past 2 weeks = 7	
9 / Symptom Frequency	Q9=Times Shortness of Breath Limit Sleep	- Every night = 1 - 3 or more times a week but not every day = 2 - 1-2 times a week = 3 - Less than once a week = 4 - Never over the past 2 weeks = 5	
4 / Symptom Burden	Q4=Bothered by Swelling in Feet/Ankles/Legs	- Extremely bothersome = 1 - Quite a bit bothersome = 2 - Moderately bothersome = 3 - Slightly bothersome = 4 - Not at all bothersome = 5 - I've had no swelling/fatigue/shortness of breath = 5	If at least one of questions Q4, Q6 and Q8 is not missing, then Symptom Burden Score is calculated as below: **Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4**

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
6 / Symptom Burden	Q6=Bothered by Fatigue	- Extremely bothersome = 1 - Quite a bit bothersome = 2 - Moderately bothersome = 3 - Slightly bothersome = 4 - Not at all bothersome = 5 - I've had no swelling/fatigue/shortness of breath = 5	
8 / Symptom Burden	Q8=Bothered by Shortness of Breath	- Extremely bothersome = 1 - Quite a bit bothersome = 2 - Moderately bothersome = 3 - Slightly bothersome = 4 - Not at all bothersome = 5 - I've had no swelling/fatigue/shortness of breath = 5	
			Total Symptom Score = mean of the following available summary scores: **Symptom Frequency Score** **Symptom Burden Score**
10 / Self-Efficacy	Q10=Know What to Do if Heart Failure Gets Worse	- Not at all sure = 1 - Not very sure = 2 - Somewhat sure = 3 - Mostly sure = 4 - Completely sure = 5	If at least one of Questions 10 and 11 is not missing, then Self-Efficacy Score is calculated as below: **Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4**
11 / Self-Efficacy	Understand Heart Failure Symptoms from Getting Worse	- Do not understand at all = 1 - Do not understand very well = 2 - Somewhat understand = 3 - Mostly understand = 4 - Completely understand = 5	

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
12/Quality of Life	Heart Failure Limited Enjoyment of Life	- It has extremely limited my enjoyment of life = 1 - It has limited my enjoyment of life quite a bit = 2 - It has moderately limited my enjoyment of life = 3 - It has slightly limited my enjoyment of life = 4 - It has not limited my enjoyment of life at all = 5	If at least one of Questions 12, 13 and 14 is not missing, then Quality of Life Score is calculated as below: **Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) − 1]/4**
13/Quality of Life	Feeling About Your Life with Heart Failure	- Not at all satisfied = 1 - Mostly dissatisfied = 2 - Somewhat satisfied = 3 - Mostly satisfied = 4 - Completely satisfied = 5	
14/Quality of Life	Feeling Discouraged/Down of Heart Failure	- I felt that way all of the time = 1 - I felt that way most of the time = 2 - I occasionally felt that way = 3 - I rarely felt that way = 4 - I never felt that way = 5	
15/Social Limitation	Q15a= Hobbies, Recreational Activities Q15b= Working or Doing Household Chores Q15c= Visiting Family or Friends Out of Home Q15d= Intimate Relationships with Loved Ones	- Severely limited = 1 - Limited quite a bit = 2 - Moderately limited = 3 - Slightly limited = 4 - Did not limit at all = 5 - Does not apply or did not do for other reasons = <missing value>	If at least two of Q15a-Q15d are not missing, then Social Limitation Score is calculated as below: **Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) − 1]/4**

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
			Overall Summary Score = mean of the following available summary scores: **Physical Limitation Score** **Total Symptom Score** **Quality of Life Score** **Social Limitation Score**
			Clinical Summary Score = mean of the following available summary scores: **Physical Limitation Score** **Total Symptom Score**

Source: KCCQ scoring instructions for Finland and Sweden.

References to "means of questions actually answered" imply the following:

- If there are n questions in a scale, and the patient must answer m to score the scale, but the patient answers only n-i, where n-i >= m, the mean of those questions should be calculated as: (sum of the responses to those n-i questions) / (n-i) [and not as (sum of the responses to those n-i questions) / n].

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KCCQ overall summary score and KCCQ physical limitation score will be of interest for this study.

6.5. Drug Concentration Measurements and Pharmacokinetic Parameters

Blood samples of approximately 2 mL will be collected for measurement for plasma concentrations of AZD4831 as specified in the Table 2. Samples will be collected, handled, labelled, stored and shipped as detailed in the laboratory manual. Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the sponsor. Diary cards will be given to the patients at the randomization visit and the patients will be asked to fill in the dose intake information (date and time) at home.

All PK, and PK modelling work will be described in a separate data analysis plan.

Full details of the analytical method used for determination of drug concentration will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

6.6. Safety Assessments

Safety assessments include AEs/SAEs including maculopapular rash grade 3, vital signs, physical examination, clinical laboratory safety evaluations (haematology, clinical chemistry and urinalysis) and ECGs.

6.6.1. Extent of Exposure and Compliance to Study Treatment

As per protocol, subjects start the study IP at the day of randomization (Visit 2). Then, randomized patients will be dispensed with one bottle of IP at each dispensing visit. Dispensation will take place at the following per-protocol study visits:

- Visit 2 (Randomization),
- Visit 3 (10 days),
- Visit 5 (30 days).

IP will be returned and accountability checked at the following visits:

- Visit 3 (10 days),
- Visit 5 (30 days),
- Visit 7 (90 days).

Dose at Visit 2, Visit 3, Visit 5, and Visit 7 will be given by study personnel at the study site. Dose at Visit 4 and Visit 6 may be given at home. The exact dose intake time will be recorded on a diary card. The diary cards will be given to the patients at the randomization

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visit and the patients will be asked to fill in the dose intake information (date and time) at home. If home visit, patient should be instructed not to take the morning dose on the same day as the visit.

All randomized patients will be dosed the first 10 days with a starting dose of ▮▮▮▮ once daily AZD4831 or matching placebo.

After 10 days, the dose will be increased to ▮▮▮ AZD4831 or matching placebo for the remaining 80 days for patients in Part A.

After 10 days, the dose will be either ▮▮▮▮▮▮ AZD4831 or matching placebo (depending on the outcome of the interim analysis in Part A) for the remaining 80 days for patients in Part B.

Study treatment will be taken orally in ▮▮▮▮ once daily as follows:

- ▮▮▮ AZD4831 or matching ▮▮▮ placebo;
- ▮▮▮ AZD4831 or matching ▮▮ placebo;
- ▮▮▮▮▮▮ AZD4831 or matching ▮▮▮▮▮ placebo;

The number of dispensed and returned ▮▮▮ and dates of dispensed and returned ▮▮▮ will be entered in eCRF.

Exposure and compliance are calculated as follow:

Exposure

Total exposure (days) will be calculated for patients in the safety analysis set as the total number of days on IP (i.e., gaps in dosing due to IP interruption will not be taken-out from the calculation). Exposure will be calculated as the IP last dose date minus IP first dose date plus one. If any of the first or last dates are missing, then imputed dates will not be used, and IP exposure will be set to missing.

For patients in Part B who have their dose increased to ▮▮▮▮, total exposure will be calculated by dose interval i.e. by low dose exposure (▮▮▮▮▮▮) and high dose exposure (▮▮▮ as follows:

Low dose exposure will be calculated as the ▮▮▮ IP first dose date minus IP first dose date. High dose exposure will be calculated as the IP last dose date minus the ▮▮▮ IP first dose date plus one. If the ▮▮▮ first dose date or the IP first dose date is missing, low dose exposure will be missing. Similarly, if the ▮▮▮ first dose date or the IP last dose date is missing high dose exposure will be missing.

Total actual exposure (days) will be calculated as the total number of days of effective IP intake (i.e., gaps in dosing due to IP interruption will be taken-out from the calculation). In

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this way, the patient's dosing can be reduced to a series of unbroken intervals within each of which exposure will be calculated as IP dose stop date minus the IP dose start date plus one. Actual exposure will be calculated as the sum of exposures over all the unbroken intervals.

If any of the start or stop dates of IP are missing for a dosing interval, study drug exposure for that interval will be set to missing. Imputed dates for first and last dose of IP will not be used.

Total actual exposure will be the sum of the non-missing exposures over the different dosing intervals.

Cumulative exposure over time (day) will also be computed based on total exposure, using the following duration (days) categories:

>=1 days,
>=10 days,
>=20 days;
>=30 days,
>=60 days,
>=90 days.

Compliance

Patients are supposed to take ▮▮▮ once daily of AZD4831 or matching placebo according to dosing schedule. However, if the dose is increased to ▮▮▮ then patients will be supposed thereafter to take ▮▮▮ once daily. Overall compliance to the dosing schedule will be examined for patients in the safety analysis set.

The percent compliance is defined as the total number of tablets consumed divided by the total number of tablets that should have been taken:

- (Total number of ▮▮▮ consumed) x 100 / (Total exposure) for patients on low dose of AZD4831 or matching placebo and
- (Total number of ▮▮▮ consumed) x 100 / [Low dose exposure + High dose exposure x 2] for patients on high dose of AZD4831 or matching placebo,

where, total number of ▮▮▮ consumed will be calculated as:

Total number of ▮▮▮ dispensed – Total number of ▮▮▮ returned.

No replacement of missing data will be performed. Therefore, if one of the total number of ▮▮▮ dispensed, total number of ▮▮▮ returned, or duration of exposure is missing the resulting compliance will be missing.

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Compliance will also be computed using the following categories:

- $< 80\%$
- $\geq 80\%$ to $< 120\%$
- $\geq 120\%$

6.6.2.   Adverse Events

Adverse Events (AEs) will be collected from the time of the first dose throughout the treatment phase and including the off-treatment phase. SAEs will be recorded from the time of signing the informed consent form.

All AEs with an onset date on or after the date of first dose will be included in the analyses. SAEs with an onset date before the date of first dose will be listed only.

AEs will be assigned to the phase where they start (See Section 6.2.3 for the definition of phases). In case of missing AE start or end date, the assignment of the AE to the phase will be performed after the imputation of the missing AE start date or end date (See Section 7.3 for the imputation methods).

The following algorithm will be used for AE assignment to phase:

If both the start date and start time of an AE are known, then:

- If the AE starts at any time prior to the time of the first dose of IP, then the AE will be assigned to the Baseline phase,
- If the AE starts on or after the time of the first dose of IP and up to 14 days after the date of the last dose of IP (inclusive), then the AE will be assigned to the On-treatment phase,
- If the AE starts at any time after the date of last dose of IP + 14 days, then the AE will be assigned to the Off-treatment phase.

If only the start date of an AE is known, and the start time of the AE is unknown, then:

- If the AE starts prior to the day of the first dose of IP, then the AE will be assigned to the Baseline phase,
- If the AE starts on or after the day of the first dose of IP and up to 14 days after the date of last dose of IP (inclusive), then the AE will be assigned to the On-treatment phase,
- If the AE starts after the date of last dose of IP + 14 days, then the AE will be assigned to the Off-treatment phase.

If the start date of an AE is completely missing, the AE should be assigned as follow:

- If the AE end date is known:
    - If the end-date is before the date of first dose of IP then the AE will be assigned to the Baseline phase,

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- If the end-date is on or after the date of first dose of IP, no assignment can be done.
- If the end-date is completely missing no assignment can be done.

Note that if the AE started in the on-treatment phase and became serious in the off-treatment phase the AE will be considered as serious from the start, i.e. in the on-treatment phase as well. The AE will be reported as one single record in the listing.

A drug-related AE is defined as any AE with a reasonable possibility of causal relationship to study treatment as assessed by the investigator or with a missing assessment of the causal relationship.

AEs which have not been assigned to any phase will not be summarized but will be listed.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher.

6.6.3. Clinical Laboratory Evaluations

Clinical chemistry, haematology and urinalysis will be performed at a central laboratory at visits indicated in Table 2. The list of clinical safety laboratory is given in Table 7 below.

Table 7: Safety Laboratory Assessments (SI units)

Panel Name	Parameter
Haematology/Haemostasis (whole blood)	B-Haemoglobin (Hb) (g/L)
	B-Leukocyte count (GI/L)
	B-Leukocyte differential count (absolute count) including Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils (GI/L)
	B-Platelet count (GI/L)
Clinical Chemistry (serum or plasma)	S-Creatinine (umol/L)
	S-Bilirubin, total (umol/L)
	S-Alkaline phosphatase (ALP) (ukat/L)
	S-Aspartate transaminase (AST) (ukat/L)
	S-Alanine transaminase (ALT) (ukat/L)
	Thyroid Stimulating Hormone (TSH) (mIU/L)
	Thyroxine (T4) (pmol/L)
	Triiodothyronine (T3) (pmol/L)
	Luteinizing Hormone (LH) (IU/L)
	Follicle-stimulating Hormone (FSH) (IU/L)
	S-Albumin (g/L)
	S-Potassium (mmol/L)

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Panel Name	Parameter
	S-Calcium, total (mmol/L)
	S-Sodium (mmol/L)
	S-Creatine kinase (CK) (ukat/L)
	Glucose (fasting) (mmol/L)
	hsCRP (mg/dL)
Urinalysis (dipstick)	U-Hb/Erythrocytes/Blood (+)
	U-Protein/Albumin (+)
	U-Glucose (+)
	Uric Acid (umol/L)

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

Unless otherwise specified, laboratory data obtained from Day 1 of IP up to 14 days after the last dose of IP (inclusive) will be considered as obtained during the on-treatment phase.

Unless otherwise specified, values below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

Baseline values and visit values are defined as in Section 6.3 and 6.2.2.

Change from baseline for haematology and clinical chemistry will be defined as the end of treatment (EOT) visit value minus the baseline visit value.

Urinalysis categorical variables will be classified as:

- Negative
- Trace
- +
- ++
- +++
- ++++

Laboratory values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on lab units reference range indicator.

Hy's law criteria will be assessed using total bilirubin, ALT and AST elevations. Elevations will be assessed using the individual highest value on-treatment and are described as follows:

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Bilirubin elevation
< 2xUpper limit of normal (ULN)
≥ 2xULN

ALT elevation
< 3xULN
≥ 3 - < 5xULN
≥5 - < 10xULN
≥10xULN

AST elevation
< 3xULN
≥ 3 - < 5xULN
≥5 - < 10xULN
≥10xULN

Potential Hy's Law is defined as AST or ALT ≥ 3xULN together with total BILI ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in ALP. The elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in BILI, but there is no specified timeframe within which the elevations in transaminases and BILI must occur.

6.6.4. Other Observations Related to Safety

Baseline values and visit values are defined as in Section 6.3 and 6.2.2.

Vital Signs
Vital signs will include BP (mmHg), pulse (bpm), weight (kg), height (cm), and body temperature (°C) and will be collected at visits indicated in Table 2. Body mass index (BMI) (kg/m2) will be computed and displayed at baseline.

BP and pulse measurements will be assessed prior to collection of laboratory tests with patient in resting semi-supine position with a completely automated device. They will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded in the eCRF.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the below normal reference ranges:

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Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 180 mmHg
Diastolic blood pressure	50 -120 mmHg
Pulse	50 - 95 bpm
Weight	40 - 150 kg
Height	145 – 220 cm
Body temperature	35.5 – 37.0 °C

Electrocardiogram (ECG)

Single 12-lead ECG will be obtained after the patient has been resting in a supine position for at least 10 minutes, at the visits outlined in Table 2. A digital ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals will be used. The investigator will record on the eCRF the overall evaluation of the ECG (normal or abnormal) and if abnormal, the reason and whether the abnormality is clinically significant or not.

Unless otherwise specified, ECGs data obtained from Day 1 of IP up to 14 days after the last dose of IP (inclusive) will be considered as obtained during the on-treatment phase.

Physical Examinations

Please refer to Section 5.

Skin Rash

Skin rash (if any) will be documented as follows: start date, severity, body surface area, anatomical site, symptoms, signs, effect on patient, medication administered. Photos (overview and detailed) should be taken. All skin rash reactions should be recorded as AEs, with the evaluation of severity as Grade 1, 2 or 3. Please refer to Appendix B9 of the CSP for further guidance on rash assessment.

6.7.   Pharmacodynamics Parameters

PD parameters are not evaluated in this study.

6.8.   Genetics

Participation in the genetic analysis is optional and patients who do not wish to participate in the genetic research may still participate in the study. See Appendix D of the CSP for Information regarding genetic research.

The genetic analysis will not be part of this SAP.

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7. STATISTICAL METHODS

7.1. General Methodology

Outputs for final analysis will be presented using AZD4831 ▮ and placebo treatment groups, unless the outcome of the interim analysis or the statistical monitoring is to decrease the dose to ▮ or increase it to ▮ in Part B. In addition, during part A, the study can be stopped, or the dose can be down adjusted to ▮ based on the outcome of the statistical monitoring. In those cases, final analyses will be presented using the following groups:

- AZD4831 ▮ (from part A), AZD4831 ▮ ▮ (from parts A and B) and placebo (all placebo matching doses from parts A and B) treatment groups if the dose is down adjusted to ▮ in part A and/or part B; or
- AZD4831 ▮ (from part A), AZD4831 ▮ (from part B) and placebo (all placebo matching doses from parts A and B) treatment groups if the dose is up adjusted to ▮ ▮ in part B.

In addition, treatment group comparisons outputs for final analysis will be displayed according to Table 8.

Table 8: Analysis according to the dose adjustment

	Main analysis	Additional analysis
No dose adjustment	AZD4831 ▮ vs. Placebo (from parts A and B)	-
Dose adjusted down	AZD4831 ▮ vs. Placebo (from parts A and B)	AZD4831 ▮ vs. Placebo (from part A)
Dose adjusted up	AZD4831 ▮ vs. Placebo (from part B)	AZD4831 ▮ vs. Placebo (from part A)

Outputs for interim analysis will be presented for AZD4831 ▮ treatment group only. In case the dose is decreased during part A, AZD4831 ▮ treatment group will also be displayed.

All efficacy (including exploratory) and safety variables will be summarized by treatment groups using descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum; geometric mean (GeoMean) and CV where applicable for continuous data and absolute and relative frequencies for categorical data).

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Data will be summarized by analysis visit including end of treatment (EOT) visit for efficacy variables and EOS visit for safety variables as applicable. Please see Section 6.2.2 for EOS and EOT visits definitions. Unscheduled visits data will be listed.

In addition, some safety variables will be analysed for the baseline, on-treatment, and off-treatment phases. Please see Section 6.2.3 for analysis phase definitions.

For continuous variables, the following will be used for the descriptive summaries and/or inferential analyses as appropriate:

- Observed values at baseline and timepoint,
- Change from baseline to timepoint defined as the timepoint value minus the baseline value,
- Percent change from baseline to timepoint defined as the exponential of the logarithm of the ratio (timepoint value (T) over the non-null baseline value (B)) minus 1 and multiplied by 100 i.e.

$$\% \ change = [e^{\log\left(\frac{T}{B}\right)} - 1] * 100$$

- Ratio (i.e. relative change) of timepoint over baseline defined as timepoint value over the non-null baseline value
- Geometric mean of the percent change from baseline will be computed as follows:

$$\text{Geomean of \% change} = [(e^{\frac{1}{n} * \Sigma_{i=1}^{n} \log\left(\frac{T_i}{B_i}\right)} - 1] * 100$$

    Where T_i = timepoint value for subject i,
        B_i = baseline value for subject i,
        n = total number of subjects

- CV (%) of percent change from baseline will be computed as follows:

$$\text{CV (\%) of \%change} = 100 * \sqrt{(e^{s^2}) - 1}$$

    Where s=standard deviation of $\log\left(\frac{T}{B}\right)$,

        T = timepoint value
        B = baseline value

Unless otherwise specified, p-values will be unadjusted, tests will be two-sided and two-sided 95% CIs will be computed. For the primary efficacy variable TE biomarker, a two-sided test will be used and for the first secondary efficacy variable CFVR, a one-sided test will be used. A closed test procedure will be applied to control the overall type 1-error rate due to multiplicity for the primary endpoint and the first secondary endpoint (See also Section 3).

All tests will be performed between AZD4831 ███ and placebo treatment group, unless the outcome of the interim analysis or the statistical monitoring is to decrease the dose to ███

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███ or increase it to ████ in Part B. In that case, the main analysis will be performed between AZD4831 ████ and placebo and; AZD4831 ████ or AZD4831 ████ and placebo (see Table 8).

Results from data that have been transformed, e.g. log-transformed, during the analysis will be back transformed to original scale.

For categorical variables and unless otherwise specified, the number and percentages of subjects by categories will be tabulated. Percentages will be calculated based on the number of subjects with no missing data, i.e., will add up to 100%. Categories with count of zero will not be displayed.

Unless otherwise specified, the analysis and presentation of efficacy variables including exploratory variables will be based on patients in the full analysis set; and the analysis and presentation of safety variables will be based on patients in the safety analysis set.

Baseline measurement is defined as the last available value among those in the Baseline visit window, prior to first dose of IP intake if nothing else is specified.

Changes from baseline, in certain categorical variables will be summarized using shift tables. The number and percent of subjects within each treatment group will be generated for each category post-baseline by baseline category.

Analysis of change from baseline or ratio of timepoint over baseline for certain efficacy variables will be performed using mixed model repeated measures (MMRM) model or analysis of covariance (ANCOVA) model where appropriate.

For MMRM, fixed factors will be treatment, visit, and treatment*visit interaction.

Visit within subject will be considered as repeated measurements. The model will use the spatial power covariance structure (SP (POW)) for unequally spaced data variance-covariance matrix as default.

In case convergence issues are encountered, the following approach will be adopted in this order:

- The compound symmetry will be used instead of SP (POW).
- The variable will be analysed using the ANCOVA model described below instead of using the MMRM model.

For ANCOVA model, the fixed factor will be treatment.

For both models, the covariates (also considered as fixed factors) will be the baseline value or log transformed baseline value where appropriate; and the atrial fibrillation status as reported in IVRS.

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If the 2 doses of AZD4831 are to be compared to placebo (i.e. AZD4831 ▮▮▮ vs placebo and AZD4831 ▮▮▮ or AZD4831 ▮▮▮ vs. placebo), they will be assessed in the same model.

Efficacy variables except primary and first secondary efficacy variables will be tested for normality by the means of Q-Q plots evaluations. The normality assessment will be performed at dry run and confirmed after unblinding.

Unless otherwise specified, the reportable results for variables normally distributed will be:

- Descriptive statistics of the variable analysed and the change from baseline for each group,
- The change from baseline (Least-Squares Means (LSMeans) and standard error (SE)) for each treatment group,
- The LSMeans difference between active group(s) and placebo together with the 95% CI of the difference and the p-value (1-sided or 2-sided as appropriate).

Unless otherwise specified, the reportable results for variables log-normally distributed will be:

- Descriptive statistics of the variable analysed and the percent change from baseline for each group
- The ratio of the timepoint value over baseline (Geometric LSMeans estimate, SE and 95% CI)
- The Estimated geometric LSMeans ratio of the active group(s) over placebo together with the 95% CI of the ratio and the p-value (1-sided or 2-sided as appropriate).

The ratio will be calculated as the exponent of the difference of the logarithmic transformations. The CI for the ratio will be calculated as the exponent of the CI of the difference of the logarithmic transformation.

In addition, and wherever appropriate, graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) / ratio over baseline over time (geometric LSmeans (two-sided 95%CI)) will be provided by treatment groups based on the results of the statistical model using the full analysis set.

For maculopapular rash grade 3 events, incidence rates will be displayed by treatment groups. Associated binomial proportion 95% CIs will be provided.

7.2.   Adjustments for Covariates

For efficacy variables (including exploratory variables) adjustment for the respective baseline value and the atrial fibrillation status (12 months prior to or at randomization) will be performed.

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7.3. Handling of Dropouts or Missing Data

Missing data will not be replaced. To handle missing data and unbalanced datasets, the efficacy variables (including exploratory variables) will be analysed using the restricted maximum likelihood (REML) estimation.

Partial and completely missing dates will be imputed for IP first dose date and IP last dose date. Partial missing dates will be imputed for AE onset date/date becomes serious and AE/CM stop date. Missing start dates for CMs will not be imputed.

Imputation rules are described below.

Imputation of IP First Dose Date:

First dose date and time are mandatory fields, and no imputations are expected. However, should the first dose date of IP be missing, it will be imputed if all the following criteria are met:

- The first dose date of IP is completely missing or partial, and
- There is at least one kit for which the amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing dispensed dates

If that is the case, the first dose date of study drug will be defined as the earliest dispensed date from the kits for which the amount of drug dispensed does not equal the amount of drug returned.

Missing start time will not be replaced.

Imputation of IP Last Dose Date:

Last dose date and time are mandatory fields, and no imputations are expected. However, should the last dose date of IP be missing, it will be imputed if all the following criteria are met:

- The last dose of IP is completely missing or partial, and
- There is at least one kit for which amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing returned dates

If that is the case at the time of interim analysis, the IP last dose will be defined as the latest dates among exposure start date, exposure end date and IP returned date.

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If that is the case at the time of final analysis, the IP last dose date will be defined as the latest IP returned date from kits for which the amount of drug dispensed does not equal the amount of drug returned.

Missing stop time will not be replaced.

Imputation of AE Onset Date and AE becomes serious date:

Missing AE onset date/AE becomes serious date (where UN, UNK and 0000 indicate unknown or missing Day and Month and Year respectively for partial missing dates; while completely missing dates would be left empty) will be imputed as follows:

- Completely missing date will not be imputed.
- If the day is missing and the month and year are different from the month and year of the first dose of IP, assume YYYY-MMM-01. If the month and year are the same as the first dose of IP month and year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date (after any imputation) is prior to the first dose of IP, then assume the end date for the onset date.
- If the month is missing and the year is different from the year of first dose of IP, assume YYYY-JAN-01 of the collected year. If the year is the same as the first dose of IP year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of IP, then assume the date of the first dose of IP. If the year is the same as the first dose of IP and the end date (after any imputation) is prior to the first dose of IP, then assume the end date for the onset date.

After applying these rules, if the imputed AE onset date is after a complete AE end date or date of death, the imputed onset date will be the same as the complete AE end date/date of death.

Imputation of AE / CM Stop Date:

Missing stop date (where UN, UNK and 0000 indicate unknown or missing Day and Month and Year respectively for partial missing dates; while completely missing date would be left empty) will be imputed as follows:

- Completely missing date will not be imputed
- If the day is missing: Assume the last day of the month
- If the month is missing: Assume YYYY-DEC-31.

If the AE/CM is ongoing, the stop date will remain missing.

After applying these rules, if the imputed AE or CM stop date is after the date of death, the imputed stop date will be the same as the date of death.

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Except for the above and unless otherwise specified, complete missing dates will not be imputed.

7.4. Interim Analyses and Data Monitoring

7.4.1. Interim Analyses

The interim analysis will be performed after all patients have been treated for approximately 30 days in Part A. The interim analysis results will be used either to identify the dose for Part B or to stop the study. The decision on dose adjustment or whether to stop the study will be based on the level of TE biomarker and the number of patients discontinued due to generalised maculopapular rash grade 3. Only patients treated with AZD4831 will be included in the analysis. The possible outcomes of the interim analysis are continue with ▮ ▮, decrease dose to ▮▮, increase dose to ▮▮ or stop the study.

Further details are provided in the SRC and DRC Charter.

The interim analysis will be executed by an independent Covance team.

Two cut-off dates will be considered for the interim analysis, one cut-off date for TE biomarker data and one cut-off date for safety data. Data collected prior to or on the TE biomarker cut-off date will be part of the TE biomarker analysis. Data collected prior to or on the safety cut-off date will be part of the remaining analysis. The TE biomarker data patients will be a subset of all randomized patients treated with AZD4831 for approximately 30 days in Part A.

7.4.2. Data Monitoring

A blinded SRC consisting of internal AZ expertise will review safety data related to rash on an ongoing basis throughout the study and give input and recommendations to a DRC.

The DRC consisting of internal AZ expertise will continuously monitor the number of patients who discontinue the study due to generalised maculopapular rash grade 3. The study will be stopped if at any time the proportion of discontinued patients on AZD4831 is above a prespecified level.

Specific details will be delineated in a SRC/DRC charter developed by AZ.

7.5. Multi-Centre Studies and Pooling of Centres

This is a multi-centre study conducted approximately in 10 sites and 5 countries. Approximately 96 patients will be randomized so at most 64 patients are exposed to AZD4831 for rash evaluation and about 53 patients on AZD4831 versus 27 patients on placebo for evaluation of the first primary endpoint and the first secondary endpoint.

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Given the above numbers, randomization was not stratified by site or country and data from all sites and countries will be pooled.

7.6.   Multiple Comparisons/Multiplicity

The primary efficacy variable TE biomarker will test the null hypothesis of equality in TE biomarker comparing AZD4831 to placebo versus the alternative hypothesis of non-equality comparing AZD4831 to placebo at 5% two-sided significance level.

The first secondary efficacy variable CFVR will test the null hypothesis of no increase in CFVR comparing AZD4831 to placebo versus the alternative hypothesis of an increase in CFVR in favor of AZD4831 compared to placebo at 5% one-sided significance level.

A closed test procedure will be applied to preserve the overall type 1-error rate at 5% due to multiplicity for the primary efficacy variable TE biomarker, and the first secondary efficacy variable, CFVR. The testing procedure will start with TE biomarker. If the null hypothesis for TE biomarker is rejected, the testing procedure shall continue with CFVR. If the null hypothesis for TE biomarker is not rejected, the testing procedure with CFVR will stop.

The testing strategy allows an outcome of success for the TE biomarker only, or success for both TE biomarker and CFVR.

Two-sided 95% CIs for TE biomarker and CFVR ratios of AZD4831 over placebo will be provided. Additionally, one-sided 95% CI will be displayed for CFVR ratio.

If the outcome of the interim analysis or the statistical monitoring is to adjust the dose in Part B, multiple comparisons will be performed (i.e AZD4831 ▇▇▇ vs placebo and; AZD4831 ▇▇▇ or AZD4831 ▇▇▇ vs placebo). However, only the dose selected for Part B (i.e. ▇▇▇ or ▇▇▇) will be of interest and as such only the comparison of AZD4831 ▇▇▇ or AZD4831 ▇▇▇ vs placebo will be of relevance (and are called in this document main analysis as opposed to additional analysis). Please see Table 8. Therefore, no adjustments for multiple comparisons is required.

7.7.   Use of an "Efficacy Subset" of Patients

Not applicable to this study.

7.8.   Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.9.   Examination of Subgroups

Not applicable to this study.

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8.   STATISTICAL ANALYSIS

8.1.   Disposition of Patients

Disposition will be summarized for all enrolled patients overall and by treatment group where appropriate.

Additionally, the number of patients included in the safety analysis set, full analysis set, PK analysis set (see Section 8.3), and the number of patients excluded from these analysis sets will be reported with a break down by reason for exclusion and by treatment group. Patients excluded from the full analysis set will be listed for all enrolled patients. Patients excluded from the safety analysis set and from the PK analysis set will be listed for the full analysis set. Patients included in safety analysis set and PK analysis set will be displayed according to actual arm while patients in full analysis set will be summarized by planned arm.

The number and percentage of patients by stratification factor ((IVRS) (Yes vs No)) will be displayed using the full analysis set.

The number and percentage of patients having substance use (alcohol, nicotine) will be provided by treatment group and overall. In addition, the number of alcohol units per frequency will be listed.

A listing of all patients who discontinued after enrolment will be provided using all enrolled patients.

A listing of randomization codes for each patient as well as the treatment group they were randomized to will be provided for the full analysis set.

A listing of patients affected by the COVID-19 pandemic will also be produced using an external file provided by AstraZeneca.

8.2.   Protocol Deviations

Important protocol deviations (IPDs) will be summarized and listed for the full analysis set.

The number and percentage of patients with at least one IPD category as well as the number and percentage of patients meeting each IPD category will be provided by treatment group and in total.

Patients meeting an IPD category more than once will be counted once for the corresponding IPD category. Any patient who have more than one IPD category will be counted once in the overall summary.

A listing of IPD categories and sub-categories will be provided for the full analysis set.

The list of IPDs is provided in the non-compliance handling plan.

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8.3. Analysis Populations

There will be 3 analysis populations defined for the study analyses.

8.3.1. Full analysis set

All patients who have been randomized to IP will be included in the full analysis set irrespective of their protocol adherence and continued participation in the study.

Patients will be analysed according to their randomized IP, irrespective of whether or not they have prematurely discontinued. Patients who withdraw consent to participate in the study are included up to the date of their study termination.

8.3.2. Safety analysis set

All patients who received at least 1 dose of randomized AZD4831 or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g. those randomized to AZD4831 but actually given placebo) will be accounted for in the actual treatment group.

In other words, if a patient receives at least one dose of AZD4831 at any time instead of placebo, then the patient will be analysed in the AZD4831 dose group for all the safety analyses. In addition, if a patient receives a higher dose of AZD4831at any time than what was intended then the patient will be analysed in the higher AZD4831 dose group for all the safety analyses.

8.3.3. PK analysis set

The PK analysis set will consist of all patients in the full analysis set who have received at least one dose of AZD4831, and who have at least one PK sample post dose.

8.4. Demographic and Other Baseline Characteristics

All demographics baseline summaries will be presented by treatment group and overall and will be based on the full analysis set unless otherwise specified. Age (years), weight (kg), height (cm) and BMI (kg/m2) will be summarized with descriptive statistics for continuous variables. Age group (<65; 65-75; >75 years), sex, race, ethnic group and country will be summarized as categorical variables.

Demographic and other baseline characteristics will be presented in listings for the full analysis set.

Patient recruitment by country and center will be summarized by treatment and overall for the full analysis set. Patient recruitment will be listed for the full analysis set.

Disease related medical history as well surgical/procedure history will be coded in MedDRA version 21.0 or higher and will be summarized by system organ class (SOC) and preferred term (PT) for the full analysis set. Patients with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Patients with events in more than one SOC/PT will be

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counted once in each of those SOC/PT. Relevant medical and surgical/procedure history will be sorted alphabetically by SOC and PT.

8.5.   Prior and Concomitant Therapy

The World Health Organization Enhanced + Herbal Dictionary (WHO-DDE + HD) Drug Dictionary version 2018Mar B3 or higher will be used to classify medications by PT and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

For the purpose of the analysis, medication will be classified as either prior or concomitant (but not both) according to its stop date. Prior medication is defined as any medication with a stop date prior to the first dose of IP (exclusive). CM is defined as any medication with a stop date on or after the first dose of IP, or any medication taken prior to IP and that is ongoing.

Note that CSP definition of CM (i.e. any medication the patient is receiving at the time of enrollment) or eCRF question "Taken prior to study?" will not be used to classify a medication as either prior or concomitant.

Imputation methods for missing medication stop dates are described in Section 7.3.

Frequency counts and percentages will be provided to summaries the use of allowed and disallowed CMs separately and using the full analysis set. The number and percentage of patients within ATC level 4 (chemical subgroup) and product name will be presented by treatment group and overall. Patients will only be counted once per ATC level 4 and product name. Allowed CMs will be sorted by decreasing incidence overall, by ATC level 4 and within that by product name.

Medications not allowed at entry and/or during the study will be flagged by data management, confirmed by Study Physician, and provided as an external file. The exhaustive list of disallowed medications (coding and indication wherever applicable) is reported in the Integrated Data Review Plan (IDRP), "Prohibited Medication" tab.

A listing of previous and CMs with ATC codes by WHO-DDE + HD preferred name, route of administration, frequency and dose, start date, duration and reason will be provided for the full analysis set.

Duration (in days) will be calculated as stop date minus start date +1. If medication start date is partially or completely missing and/or stop date is completely missing duration will be missing.

8.6.   Analysis of Efficacy Parameters

Unless otherwise specified, the following efficacy (including exploratory) analyses will be based using the full analysis set. In addition, efficacy data will be presented in listing format for the full analysis set.

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8.6.1. Analysis of Primary Efficacy Variable

The primary efficacy variable is the percent change from baseline to EOT in TE biomarker. TE biomarker will be summarized descriptively as continuous variables at each visit and percent changes from baseline. Summaries will be presented by treatment group using the full analysis set.

The primary efficacy variable will test the null hypothesis of equality in TE biomarker at EOT comparing AZD4831 to placebo versus the alternative hypothesis of non-equality at EOT comparing AZD4831 to placebo at 5% two-sided significance level.

The MMRM model described in section 7.1 will be used to assess the primary objective using the full analysis set. It will model the ratio of timepoint over baseline. Two-sided 95% CIs and two-sided p-value will be provided for TE biomarker ratio of AZD4831 over placebo comparing EOT to baseline.

The reportable results will be those for the log-normal variables.

Graphical representations of the ratio of the timepoint value over baseline (geometric LSmeans (two sided 95%CI)) over time will be provided by treatment group using the full analysis set.

8.6.2. Analysis of Secondary Efficacy Variables

CFVR

The first secondary efficacy variable is the percent change from baseline to EOT in CFVR.

CFVR will be summarized descriptively as continuous variables at each visit and percent changes from baseline. Summaries will be presented by treatment group using the full analysis set.

The first secondary efficacy variable CFVR will test the null hypothesis of no increase in CFVR from baseline to EOT comparing AZD4831 to placebo versus the alternative hypothesis of an increase in CFVR from baseline to EOT in favor of AZD4831 compared to placebo at 5% one-sided significance level.

The ANCOVA model described in Section 7.1 will be used to assess the first secondary objective using the full analysis set. It will model the ratio of timepoint over baseline. One-sided 95% CI and one-sided p-value will be provided for CFVR ratio of AZD4831 over placebo comparing EOT to baseline. Additionally, a two-sided test will be performed.

Graphical representations of the ratio of the timepoint value over baseline (geometric LSmeans (two-sided 95%CI)) over time will be provided by treatment group using the full analysis set.

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6MWT

6MWT (cumulative walking distance) will be summarized descriptively as continuous variables at each visit and change from baseline. Summaries will be presented by treatment group using the full analysis set.

Cumulative walking distance will be analysed for changes from baseline at EOT using the full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits.

The reportable results will be those for normal variables.

Graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) will be provided by treatment group using the full analysis set.

PK

Refer to section 8.6.4.

8.6.3.   Analysis of Exploratory Variables

Echocardiography (E/e', LAVI, GLS, right ventricular free wall longitudinal strain and left atrium reservoir strain)

Standard echocardiography (E/e' at rest and LAVI at rest and at hyperaemia) and strain imaging echocardiography (GLS at rest and at hyperaemia, right ventricular free wall longitudinal strain at rest and at hyperaemia and left atrium reservoir strain at rest and at hyperaemia) data will be summarized descriptively as continuous variables at each visit and change from baseline or percent change from baseline as appropriate. Summaries will be presented by treatment group using the full analysis set.

Standard echocardiography and strain imaging echocardiography data will be analysed for changes from baseline or percent changes from baseline as appropriate at EOT using the full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits for all parameters measured at rest. The ANCOVA model described in section 7.1 will be used for the parameters measured at hyperaemia.

The reportable results will be those for normal or log normal variables depending on the outcome of the normality assessments except for GLS and right ventricular free wall longitudinal strain at rest and at hyperaemia which will be considered as normally distributed as the expected results are negative.

Depending on the normality assessment, graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) / ratio of the timepoint value over baseline over time (geometric LSmeans (two-sided 95%CI)) will be provided by treatment group using the full analysis set.

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cfPWV and bPWA

cfPWV and bPWA will be summarized descriptively as continuous variables at each visit and change from baseline or percent change from baseline as appropriate. Summaries will be presented by treatment group using the full analysis set.

cfPWV and bPWA will be analysed for changes from baseline or percent changes from baseline as appropriate at EOT using the full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits.

The reportable results will be those for normal or log normal variables depending on the outcome of the normality assessments.

Depending on the normality assessment, graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) / ratio of the timepoint value over baseline over time (geometric LSmeans (two-sided 95%CI)) will be provided by treatment group using the full analysis set.

Endothelial function measurement -EndoPAT™

EndoPAT includes measurement of RHI.

EndoPAT will be summarized descriptively as continuous variables at each visit and change from baseline or percent change from baseline as appropriate. Summaries will be presented by treatment group using the full analysis set.

EndoPAT will be analysed for changes from baseline or percent changes from baseline as appropriate at EOT using the Full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits.

The reportable results will be those for normal or log normal variables depending on the outcome of the normality assessments.

Depending on the normality assessment, graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) / ratio of the timepoint value over baseline over time (geometric LSmeans (two-sided 95%CI)) will be provided by treatment group using the full analysis set.

NT-proBNP

NT-proBNP will be summarized descriptively as continuous variables at each visit and percent change from baseline. Summaries will be presented by treatment group using the full analysis set.

NT-proBNP will be analysed for percent changes from baseline to EOT using the full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits.

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The reportable results will be those for log normal variables.

Graphical representations of the ratio of the timepoint value over baseline over time (geometric LSmeans (two-sided 95%CI)) will be provided by treatment group using the full analysis set.

Lipids and other laboratory assessments

Lipids and other laboratory assessments will be summarized descriptively as continuous variables at each visit and change from baseline. Summaries will be presented by treatment group using the full analysis set.

Patient Reported Outcome Questionnaire (KCCQ)

KCCQ overall summary score and KCCQ physical limitation score will be summarized descriptively as continuous variables at each visit and changes from baseline. Summaries will be presented by treatment group using the full analysis set.

In addition, KCCQ overall summary score and KCCQ physical limitation score will be analysed for change from baseline to EOT and change from baseline to EOS using the full analysis set. The MMRM model described in section 7.1 will be used with available data from all intermediate analysis visits to compare the treatment groups at EOT and EOS.

The reportable results will be those for normal variables.

Graphical representations of the change from baseline over time (LSmeans (two-sided 95% CI)) will be provided by treatment group using the full analysis set.

8.6.4.   Analysis of Pharmacokinetic Variables

PK variables will be provided in a separate report.

8.6.5.   Subgroup Analyses

No subgroup analyses of efficacy data are planned.

8.6.6.   Exploratory Analyses

See efficacy analyses sections.

8.7.   Analysis of Safety

8.7.1.   Extent of Exposure and Compliance to Study Treatment

Exposure and compliance are calculated as described in section 6.6.1.

Extent of Exposure

Total exposure (days) and cumulative exposure over time (days) will be summarized by treatment group using the safety analysis set.

Total exposure and total actual exposure will be listed for the safety analysis set.

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Measurements of Treatment Compliance

Both, overall compliance and by categories will be summarized by treatment group and overall, based on the safety analysis set.

Compliance will be listed for the safety analysis set.

8.7.2. Adverse Events

Unless specified otherwise, AEs will be summarized using the safety analysis set by treatment group and treatment phase as defined in Section 6.6.2 for the on-treatment and off-treatment phases as described below.

An overview table for all the AEs will be produced including the number of patients with any AE, any AE with outcome of death, any SAE, any AE leading to dose interruption, any AE leading to withdrawal from study. The number and percentage of patients with AEs in any category will be produced.

The number and percentage of patients with AEs occurring with a frequency>5.0% in any treatment group will be displayed for each PT.

Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs.

The number and percentage of patients with any AEs will be displayed for each SOC and within each SOC by PT.

The number and percentage of patients with any AEs will be displayed by PT and maximum reported intensity.

The number and percentage of patients with any AEs will be displayed by PT and investigator's causality assessment.

For the summary of AEs by PT and maximum intensity, if a patient has multiple events occurring in same PT within a treatment phase, then the event with the highest intensity will be counted. For the summary of AEs by PT and investigator's causality assessment, if a patient has multiple events occurring in same PT within a treatment phase, then the event with the maximum reported causality will be counted.

The number of AEs and SAEs will be displayed by SOC and PT.

The number and percentage of patients with AEs (for both Safety analysis set and Full analysis set) with outcome of death and SAEs (Safety analysis set) will be also displayed by SOC and PT.

The number and percentage of patients with AEs leading to discontinuation of IP will be displayed by SOC and PT for on-treatment phase only.

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In addition, a list of key patient information for patients with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP will be provided, including age, sex, reported and PT and data related to the event.

Time from first dose to AE (in days) will be calculated as the AE start date minus date of first dose +1. Time from last dose to death (in days) will be calculated as the date of death minus date of last dose +1. Time from first dose to death (in days) will be calculated as the date of death minus date of first dose +1.

Time from start of treatment to onset of AE will be calculated as start date of the AE minus date of first dose +1.

Time from last dose prior to AE start date will be calculated only for AEs starting after the discontinuation of the study treatment. It will be calculated as start date of the AE minus date of last dose +1.

Time from start of treatment to becoming serious will be calculated as date in which the AE met criteria for serious AE minus date of first dose +1.

Time from start of treatment to discontinuation will be calculated as discontinuation date minus start of treatment date +1.

If one of the dates required for time calculation (after date imputation as described in Section 7.3) is missing or partial, corresponding time will be missing.

The number and percentage of patients with non-serious AEs occurring with a frequency>5.0% in any treatment group will be displayed by SOC and PT. These outputs will be provided in a separate document and will not be part of the clinical study report.

The number and percentage of patients with generalised maculopapular rash will be displayed by CTCAE grade.

In addition, the patients who discontinue due to generalised maculopapular rash grade 3 will be presented as point estimate of incidence rate by treatment group together with 95% CI.

Listings will be presented by patient for all AEs using the safety analysis set. Duration (day) will be calculated as stop date minus start date +1. Duration will be calculated only for complete dates (not imputed).

8.7.3.   Clinical Laboratory Evaluations

Laboratory test results for haematology and clinical chemistry will be summarized in SI units with n, mean, median, SD, minimum, and maximum for each treatment group and at each visit.

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Change from baseline for haematology and clinical chemistry will be defined as each visit value minus the baseline visit value.

For urinalysis laboratory parameters, shifts from baseline to maximum value during treatment will be provided. Only those subjects who have both a baseline value and at last one on-treatment value will be included. Urinalysis continuous variables will also be summarized over time.

Hy's Law criteria will also be summarized using the safety analysis set.

Patients with potential Hy's Law will be provided in listing format for the safety analysis set.

All clinical laboratory data will be presented in listings for the safety analysis set and within each listing, quantitative laboratory values outside the normal ranges will be flagged.

8.7.4.   Other Observations Related to Safety

Vital Signs

Vital signs (blood pressure, pulse, weight and body temperature) will be summarized descriptively as continuous variables with n, mean, SD, minimum, median and maximum, at each visit and for change from Baseline to each visit by treatment group using the safety analysis set.

Vital signs data will also be listed using the safety analysis set.

Electrocardiogram

Shifts from baseline to last observation on-treatment in ECG overall evaluation will be analysed in terms of normality and clinical significance. Summaries will be provided by treatment group using safety analysis set. ECG data will be listed using the safety analysis set.

Unless otherwise specified, ECGs data obtained from Day 1 of IP up to 14 days after the last dose of IP (inclusive) will be considered as obtained during the on-treatment phase.

8.8.   Pharmacodynamics

PD parameters are not evaluated in this study.

8.9.   Interim Analysis

Safety, tolerability and TE biomarker will be evaluated in the interim analysis. Safety and tolerability will be assessed for patients in the safety analysis set and TE will be assessed for the full analysis set. Only data from AZD4831 treatment group will be used in the interim outputs (using ███ group only; or ███ and ███ dose groups in case the dose is down adjustment following the outcome of the statistical monitoring). Data from the placebo group will not be displayed in the interim outputs.

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Only descriptive analyses for the AZD4831 treatment group will be presented and thus no adjustments to the overall type 1 error is required.

The interim analyses will include a description of the patient disposition, TE biomarker, safety and general tolerability including generalised maculopapular rash grade 3.

8.9.1. Disposition and demographic characteristics

Disposition of patients will be described descriptively as detailed in section 8.1, for patients in the full analysis set. PK set will not be included in the output for the interim analysis.

Important protocol deviations will be summarized descriptively as described in section 8.1.

8.9.2. Efficacy assessment

TE biomarker will be summarized with descriptive statistics over time (including Visit 2, Visit 3, Visit 5 and Visit 7) using the full analysis set. Individual values will also be listed.

8.9.3. Safety assessment

Compliance and exposure

Compliance and exposure will be summarized descriptively as described in section 6.6.1 using the safety analysis set.

Adverse events

The number and percentage of patients with AEs in any category will be produced using the safety analysis set for the on-treatment and off-treatment phases.

The number and percentage of patients with any AEs will be displayed for each SOC and within each SOC by PT for both phases. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs.

The number and percentage of patients with AEs leading to discontinuation of IP will be displayed by SOC and PT for on-treatment phase only.

The number and percentage of patients with generalised maculopapular rash will be displayed by CTCAE grade.

In addition, the patients who discontinue due to generalised maculopapular rash grade 3 will be presented as point estimate of incidence rate together with 95% CI.

AEs will be listed using the safety analysis set.

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Clinical laboratory evaluation

Laboratory test results for haematology and clinical chemistry will be summarized in SI units with n, mean, median, SD, minimum, and maximum for each treatment group and at each visit.

Change from baseline for haematology and clinical chemistry will be defined as each visit value minus the baseline visit value.

For urinalysis laboratory parameters, shifts from baseline to maximum value during treatment will be provided. Only those subjects who have both a baseline value and at least one on-treatment value will be included. Urinalysis continuous variables will also be summarized over time.

All clinical laboratory data will be presented in listings for the safety analysis set and within each listing, quantitative laboratory values outside the normal ranges will be flagged.

9. Computer Software

All analyses will be performed by Chiltern International using Version 9.4 or later of statistical analysis software SAS®. All summary tables, figures and data listings will be prepared using SAS® software.

The standard operating procedures (SOPs) of Chiltern International will be followed in the creation and quality control of all data displays and analyses.

10. References

C.Patrick Green, Charles B. Porter, Dennis R. Bresnahan, John A. Spertus. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure, Journal of the American College of Cardiology, Volume 35, Issue 5, 2000, Pages 1245-1255.

11. Appendices

Appendix 1 VARIABLE DEFINITIONS

Assessment of variable not already explicated in the text are reported below:

Age will be calculated as the informed consent date minus the date of birth divided by 365.25 [Age=(ICF Date-Date of birth)/365.25].

Age group will be displayed for the following 3 categories: <65; >=65 -<=75; >75 years.

BMI (kg/m2) is calculated as: weight (kg) / [height (m)]^2, rounded to two decimal place.

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Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm) and temperature in degree Celsius (°C).

Appendix 2   STATISTICAL ANALYSIS AND PROGRAMMING DETAILS

General guidance about the display can be found in the shells.

12.   Table shells and specifications

TFL number	Title	Standard	Interim	HLR
Section 14.1 Demographic, baseline, concomitant medication and other subject-specific characteristics				
Table 14.1.1	Subject disposition (All Subjects)	SP1	X	X
Table 14.1.2	Important protocol deviations (Full analysis set)	SP2	X	X
Table 14.1.3	Analysis sets	SP3	X	X
Table 14.1.4	Demographic characteristics (Full analysis set)	SP4		
Table 14.1.5	Disease related medical history (Full analysis set)	SP7(i)		
Table 14.1.6	Surgical and procedure history (Full analysis set)	SP7(ii)		
Table 14.1.7	Subject characteristics (Full analysis set)	SP8		
Table 14.1.8	Disallowed concomitant medications during study (Full analysis set)	SP9		
Table 14.1.9	All allowed concomitant medications during study (Full analysis set)	SP10		
Table 14.1.10	Study treatment compliance (Safety analysis set)	SP11	X	X
Table 14.1.11	Subject recruitment by country and centre (Full analysis set)	ASP1		
Table 14.1.12	Substance use and consumption, categorized (Full analysis set)	ASP2(subst)		
Table 14.1.13	Stratification factors recorded at randomization by IVRS (Full analysis set)	ASP6		
Section 14.2 Efficacy assessments				

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TFL number	Title	Standard	Interim	HLR
14.2.1 Primary and secondary efficacy assessments				
Table 14.2.1.1	Efficacy variables, overview of key results (Full analysis set)	E1		X
Table 14.2.1.2	TE biomarker by visit, summary statistics (Full analysis set)	EF_T1b	X	X
Table 14.2.1.3	TE biomarker relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2b		X
Table 14.2.1.4	Coronary flow velocity reserve (CFVR) by visit, summary statistics (Full analysis set)	EF_T1b		
Table 14.2.1.5	Coronary flow velocity reserve (CFVR) relative change from baseline to end of treatment, treatment comparisons, ANCOVA (Full analysis set)	EF_T2b(CFVR)		X
Table 14.2.1.6	6 Minutes walking test (6MWT), cumulative walking distance by visit, summary statistics (Full analysis set)	EF_T1a		
Table 14.2.1.7	6 Minutes walking test (6MWT), cumulative walking distance change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a		X
14.2.2 Exploratory assessments				
Table 14.2.2.1	Standard echocardiography assessments by visit, E/e' summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.2	Standard echocardiography assessments, E/e' change from baseline / relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a/b		
Table 14.2.2.3.1	Standard echocardiography assessments by visit, LAVI at rest summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.3.2	Standard echocardiography assessments by visit, LAVI at hyperaemia summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.4.1	Standard echocardiography assessments, LAVI at rest change from baseline / relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a/b		
Table 14.2.2.4.2	Standard echocardiography assessments, LAVI at hyperaemia change from baseline / relative change from baseline to end of treatment, treatment comparisons ANCOVA (Full analysis set)	EF_T2a/b		

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Table 14.2.2.5.1	Strain imaging echocardiography assessments by visit, GLS at rest summary statistics (Full analysis set)	EF_T1a		
Table 14.2.2.5.2	Strain imaging echocardiography assessments by visit, GLS at hyperaemia summary statistics (Full analysis set)	EF_T1a		
Table 14.2.2.6.1	Strain imaging echocardiography assessments, GLS at rest change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a		
Table 14.2.2.6.2	Strain imaging echocardiography assessments, GLS at hyperaemia change from baseline to end of treatment, treatment comparisons ANCOVA (Full analysis set)	EF_T2a		
Table 14.2.2.7.1	Strain imaging echocardiography assessments by visit, right ventricular free wall longitudinal strain (RVFWLS) at rest summary statistics (Full analysis set)	EF_T1a		
Table 14.2.2.7.2	Strain imaging echocardiography assessments by visit, right ventricular free wall longitudinal strain (RVFWLS) at hyperaemia summary statistics (Full analysis set)	EF_T1a		
Table 14.2.2.8.1	Strain imaging echocardiography assessments, right ventricular free wall longitudinal strain at rest change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a		
Table 14.2.2.8.2	Strain imaging echocardiography assessments, right ventricular free wall longitudinal strain at hyperaemia change from baseline to end of treatment, treatment comparisons ANCOVA (Full analysis set)	EF_T2a		
Table 14.2.2.9.1	Strain imaging echocardiography assessments by visit, left atrium reservoir strain at rest summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.9.2	Strain imaging echocardiography assessments by visit, left atrium reservoir strain at hyperaemia summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.10.1	Strain imaging echocardiography assessments, left atrium reservoir strain at rest change from baseline / relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a/b		
Table 14.2.2.10.2	Strain imaging echocardiography assessments, left atrium reservoir strain at hyperaemia change from baseline / relative change from baseline to end of treatment, treatment comparisons ANCOVA (Full analysis set)	EF_T2a/b		

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Table 14.2.2.11	Carotid-femoral pulse wave velocity (cfPWV) and brachial Pulse Wave Analysis (bPWA) by visit – normal variables, summary statistics (Full analysis set)	EF_T1a(mult)		
Table 14.2.2.12	Carotid-femoral pulse wave velocity (cfPWV) and brachial Pulse Wave Analysis (bPWA) by visit – log-normal variables, summary statistics (Full analysis set)	EF_T1b(mult)		
Table 14.2.2.13	Carotid-femoral pulse wave velocity (cfPWV) and brachial Pulse Wave Analysis (bPWA) change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a(mult)		
Table 14.2.2.14	Carotid-femoral Pulse Wave Velocity (cfPWV) and brachial Pulse Wave Analysis (bPWA) relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2b(mult)		
Table 14.2.2.15	Peripheral endothelial function by visit, RHI summary statistics (Full analysis set)	EF_T1a/b		
Table 14.2.2.16	Peripheral endothelial function, RHI change from baseline/relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a/b		
Table 14.2.2.17	NT-proBNP by visit, summary statistics (Full analysis set)	EF_T1b		
Table 14.2.2.18	NT-proBNP relative change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2b		
Table 14.2.2.19	Kansas City Cardiomyopathy Questionnaire (KCCQ) by visit, summary statistics (Full analysis set)	EF_T1a(mult)		
Table 14.2.2.20	Kansas City Cardiomyopathy Questionnaire (KCCQ) change from baseline to end of treatment, treatment comparisons MMRM (Full analysis set)	EF_T2a(mult)		
Table 14.2.2.21	Kansas City Cardiomyopathy Questionnaire (KCCQ) change from baseline to end of study, treatment comparisons MMRM (Full analysis set)	EF_T2a(mult)		
Table 14.2.2.22	Lipid status assessments and other laboratory assessments by visit, summary statistics (Full analysis set)	S25(lip)		
Section 14.2 Primary, Secondary and Exploratory Efficacy assessments Figures				
Figure 14.2.1.1	TE biomarker relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		

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Figure 14.2.1.2	Coronary flow velocity reserve (CFVR) relative change from baseline by visit, ANCOVA, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.1.3	6 Minutes walking test (6MWT), cumulative walking distance change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.1	Standard echocardiography assessments, E/e' change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.2.1	Standard echocardiography assessments, LAVI at rest change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.2.2	Standard echocardiography assessments, LAVI at hyperaemia change from baseline by visit, ANCOVA, LSmeans (two-sided 95% CI) / relative change from baseline by visit, ANCOVA, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.3.1	Strain imaging echocardiography assessments, GLS at rest change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.3.2	Strain imaging echocardiography assessments, GLS at hyperaemia change from baseline by visit, ANCOVA, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.4.1	Strain imaging echocardiography assessments, right ventricular free wall longitudinal strain at rest change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.4.2	Strain imaging echocardiography assessments, right ventricular free wall longitudinal strain at hyperaemia change from baseline by visit, ANCOVA, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.5.1	Strain imaging echocardiography assessments, left atrium reservoir strain at rest change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		

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Figure 14.2.2.5.2	Strain imaging echocardiography assessments, left atrium reservoir strain at hyperaemia change from baseline by visit, ANCOVA, LSmeans (two-sided 95% CI) / relative change from baseline by visit, ANCOVA, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.6	CfPWA and bPWA, augmentation index change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.7	CfPWA and bPWA, carotid-femoral pulse wave velocity change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.8	CfPWA and bPWA, pulse pressure amplification change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.9	CfPWA and bPWA, central pulse pressure change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.10	CfPWA and bPWA, central blood pressure systolic change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.11	CfPWA and bPWA, central blood pressure diastolic change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.12	CfPWA and bPWA, brachial blood pressure systolic change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.13	CfPWA and bPWA, brachial blood pressure diastolic change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		

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Figure 14.2.2.14	Peripheral endothelial function, RHI change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) / relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.15	NT-proBNP relative change from baseline by visit, MMRM, geometric LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.16	Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Figure 14.2.2.17	Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitation score change from baseline by visit, MMRM, LSmeans (two-sided 95% CI) (Full analysis set)	E4(F)		
Section 14.3 Safety and tolerability data				
Table 14.3.1.1	Duration of exposure and cumulative exposure over time (Safety analysis set)	S1	X	X
14.3.2 All adverse events				
Table 14.3.2.1	Adverse events in any category – on-treatment phase (Safety analysis set)	S5	X	X
Table 14.3.2.2	Adverse events in any category – off-treatment phase (Safety analysis set)	S5	X	
Table 14.3.2.3	Number of subjects with adverse events, most common (frequency of >5%) – on-treatment phase (Safety analysis set)	S8		
Table 14.3.2.4	Number of subjects with adverse events, most common (frequency of >5%) – off-treatment phase (Safety analysis set)	S8		
Table 14.3.2.5	Number of subjects with adverse events by system organ class and preferred term – on-treatment phase (Safety analysis set)	S9(i)	X	
Table 14.3.2.6	Number of subjects with adverse events by system organ class and preferred term – off-treatment phase (Safety analysis set)	S9(i)	X	
Table 14.3.2.7	Number of subjects with adverse events, by preferred term and maximum reported intensity – on-treatment phase (Safety analysis set)	S10		
Table 14.3.2.8	Number of subjects with adverse events, by preferred term and maximum reported intensity – off-treatment phase (Safety analysis set)	S10		

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Table 14.3.2.9	Number of subjects with adverse events, by preferred term and causality as judged by investigator – on-treatment phase (Safety analysis set)	S11		
Table 14.3.2.10	Number of subjects with adverse events, by preferred term and causality as judged by investigator – off-treatment phase (Safety analysis set)	S11		
Table 14.3.2.11	Number of adverse events, by system organ class and preferred term – on-treatment phase (Safety analysis set)	S16(i)		
Table 14.3.2.12	Number of adverse events, by system organ class and preferred term – off-treatment phase (Safety analysis set)	S16(i)		
Table FDAAA1	Non-serious adverse events occurring in greater than 5% of subjects – on-treatment phase (Safety analysis set)	FDAAA1	X	
Table FDAAA2	Non-serious adverse events occurring in greater than 5% of subjects – off-treatment phase (Safety analysis set)	FDAAA1	X	
14.3.3 Deaths				
Table 14.3.3.1	Number of subjects with adverse events with outcome of death, by system organ class and preferred term – on-treatment phase (Safety analysis set)	S13(i)		
Table 14.3.3.2	Number of subjects with adverse events with outcome of death, by system organ class and preferred term – off-treatment phase (Safety analysis set)	S13(i)		
Table 14.3.3.3	Adverse events with outcome of death - key subject information (Safety analysis set)	S14		
14.3.4 Serious adverse events				
Table 14.3.4.1	Number of serious adverse events, by system organ class and preferred term – on-treatment phase (Safety analysis set)	S16(ii)		
Table 14.3.4.2	Number of serious adverse events, by system organ class and preferred term – off-treatment phase (Safety analysis set)	S16(ii)		
Table 14.3.4.3	Number of subjects with serious adverse events, by system organ class and preferred term – on-treatment phase (Safety analysis set)	S17(i)	X	X
Table 14.3.4.4	Number of subjects with serious adverse events, by system organ class and preferred term – off-treatment phase (Safety analysis set)	S17(i)	X	

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Table 14.3.4.5	Serious adverse events - key subject information (Safety analysis set)	S18		
14.3.5 Discontinuation of investigational product due to adverse events				
Table 14.3.5.1	Number of subjects with adverse events leading to discontinuation of investigational product, by system organ class and preferred term (Safety analysis set)	S19(i)	X	X
Table 14.3.5.2	Adverse events leading to discontinuation of investigational product – key subject information (Safety analysis set)	S20		
14.3.6 Other significant adverse events				
Table 14.3.6.1	Other significant adverse events, by category – on-treatment phase (Safety analysis set)	S21	X	
Table 14.3.6.2	Other significant adverse events, by category – off-treatment phase (Safety analysis set)	S21	X	
Table 14.3.6.3	Incidence rate of subjects who discontinue due to generalised maculopapular rash grade 3 (Safety analysis set)	E5	X	
14.3.7 Clinical laboratory evaluation				
Table 14.3.7.1	Haematology and clinical chemistry laboratory variables over time (Safety analysis set)	S25(lab)	X	
Table 14.3.7.2	Urinalysis variables over time (Safety analysis set)	S25(urin)	X	
Table 14.3.7.3	Urinalysis, baseline versus maximum value on treatment, shift table (Safety analysis set)	S33	X	
Table 14.3.7.4	Subjects with potential Hy's Law - individual subject data (Safety analysis set)	S32		
Table 14.3.7.5	Maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria (Safety analysis set)	AS14		
14.3.8 Vital signs, ECG, physical findings and other observations				
Table 14.3.8.1	Vital signs variables over time (Safety analysis set)	S25(vital)		
Table 14.3.8.2	ECG, baseline versus last observation on treatment (Safety analysis set)	S41(ecg)		
16.2 Subject Data Listings				

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Appendix 16.1.7	Randomization scheme and codes	APL23		
Appendix 16.2.1.1	Discontinued subjects	APL01		
Appendix 16.2.1.2	Subjects affected by the COVID-19 pandemic	APL-COVID1		
Appendix 16.2.2.1	Subjects with important protocol deviations	APL03		
Appendix 16.2.3.1	Subjects excluded from the full analysis set (All Subjects)	APL04		
Appendix 16.2.3.2	Subjects excluded from the safety analysis set (Full analysis set)	APL04		
Appendix 16.2.3.3	Subjects excluded from the PK analysis set (Full analysis set)	APL04		
Appendix 16.2.4.1	Demographic and baseline characteristics (Full analysis set)	APL06		
Appendix 16.2.4.2	Alcohol use (Full analysis set)	APL07 (alco)		
Appendix 16.2.4.3	Concomitant medication on entry and during the study (Full analysis set)	APL08		
Appendix 16.2.5.1	Administration of investigational product (Safety analysis set)	APL09		
16.2.6 Individual efficacy and pharmacokinetic response data				
Appendix 16.2.6.1	Efficacy assessments (Full analysis set)	APL11	X Only TE biomarker	X
Appendix 16.2.6.2	Efficacy laboratory assessments, lipid status assessments and other laboratory assessments (Full analysis set)	APL17		
16.2.7 Adverse event listing, by subject				
Appendix 16.2.7.1	Adverse events (Safety analysis set)	APL14	X	
Appendix 16.2.7.2	Adverse events for enrolled but not randomized subjects and for subjects who were not exposed to treatment	APL15		
Appendix 16.2.8.1	Laboratory safety variables (Safety analysis set)	APL16	X	X
Appendix 16.2.9.1	Individual vital signs data (Safety analysis set)	APL18		

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Appendix 16.2.10.1	Abnormalities in electrocardiogram (Safety analysis set)	APL20		

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