Clinical Study Protocol	
Study Intervention	AZD4831
Study Code	D6580C00010
Version	5.0 (Amendment Number 4.0)
Date	23 September 2022

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

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Regulatory Agency Identifier Number(s): EudraCT 2020-005844-4 ; IND 134026

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results ar disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D6580C00010

Amendment Number: 4

Study Intervention: AZD4831

Study Phase: 2b/3

Short Title: A Sequential Phase 2b and Phase 3 Study to Evaluate the Efficacy and Safety of AZD4831 in Participants with Heart Failure with Left Ventricular Ejection Fraction > 40%

Acronym: **ENDEAVOR** *(**E**fficacy a**N**d safety of AZD4831 a**D**minist**E**red for up to 48 weeks in p**A**rticipants with heart failure with left **V**entricular ejection fracti**O**n > fo**R**ty%)*

Study Physician Name and Contact Information will be provided separately

International co-ordinating investigator

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 5 (Amendment 4)	23 September 2022
Version 4 (Amendment 3)	09 February 2022
Version 3 (Amendment 2)	01 November 2021
Version 2 (Amendment 1)	25 May 2021
Version 1 (Original Protocol)	18 February 2021

Amendment 4 (23 September 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

To change the Part B study design regarding the duration of the treatment, number of participants and their allocation to treatment groups. All changes and the rationale are listed below, except for the minor changes that are introduced throughout the document to meet the standards of sponsor housestyle.

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Objective and Endpoints Table, Part B	Changed text to improve clarity. Assessment of Pharmacokinetics as a Secondary objective has been removed.	Clarification of the Section 3. Assessment of Pharmacokinetics has been moved to Tertiary objectives to reflect the changes in the study design for Part B.	Non-substantial
Section 1.1 Synopsis, Overall Design	Added text	The text has been added since it was missing in the version 4 of the CSP	Non-substantial
Section 1.1 Synopsis, Number of Participants Table	Changed text for Part B regarding the number of enrolled, randomised and participants with complete safety data data.	To reflect changes in study design for Part B	Substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Intervention Groups and Duration	Changed text regarding Part B (allocation 1:1, flexible treatment duration).	Clarification To reflect changes in study design for Part B	Substantial
Section 1.1 Synopsis, Data Monitoring Committee	Changed text: When all participants in Part A have completed Week 52, the Part A will be analysed as final interim analysis.	Clarification	Non-substantial
Section 1.1 Synopsis, Statistical Methods	Changed text regarding Part B.	To reflect changes in study design for Part B	Substantial
Section 1.2 Schema, Figure 2, Study Design – Part B	New Figure Additional footnotes	To reflect changes in study design for Part B (remote visits have been removed).	Substantial
Section 1.3 Schedule of Activities, Table 1, Part A	In footnote ‘e’ the sentence ‘At baseline orthostatic BP will also be measured 1-2 hours post dose’ has been removed.	To reflect changes in study design for Part A.	Non-substantial
Section 1.3 Schedule of Activities, Table 2, Part B	New Figure	To reflect changes in study design for Part B.	Substantial
Section 2.3.1 Risk Assessment, Table 3	Added/removed and edited text Potential risk of clinical significance: Ovarian interstitial gland vacuolation in rats has been removed. Renal toxicity has been added.	To reflect the most recent data presented in IB.	Substantial
Section 3.1 Part A	New text (KCCQ comparison of remote and on-site results).	Clarification	Non-substantial
Section 3 Objective and Endpoints, 3.2 Part B, Table 5	Changed text to improve clarity. CCI [redacted]	Clarification Changes in the study design for Part B.	Non-Substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
	CCI [redacted].		
Section 4.1 Overall Design	Changed text regarding Part B (allocation, flexible treatment duration, number of participants).	To reflect changes in study design for Part B.	Substantial
Section 4.2 Scientific rationale for study design	Changed text in the first paragraph.	To reflect changes in Inclusion criteria for both Part A and Part B	Non-substantial
Section 4.4 End of Study Definition	Added text (third paragraph) regarding Part B. Added text regarding Clinical Trial Transparency (CTT).	To reflect changes in study design for Part B.	Substantial
Section 5 Study Population, 5.1.1 Inclusion criteria - Part A	Inclusion criterion 9. Changed text	Clarification	Non-substantial
Section 5.1 Inclusion Criteria	Additional sections (5.1.1 and 5.1.2) have been created to present inclusion criteria for Part A and Part B separately.	To improve readability of the document considering differences in inclusion criteria for Part A and Part B.	Substantial
Section 5.2.1 Exclusion criteria – Part A	Text has been added/edited to clarify exclusion criteria 10, 11, 13, 15, 19, 20, 23 and 25.	Clarification	Non-substantial
Section 5.2 Exclusion criteria	Additional sections (5.2.1 and 5.2.2) have been created to present exclusion criteria for Part A and Part B separately .	To improve readability of the document considering differences in exclusion criteria for Part A and Part B.	Substantial
Section 5.4 Screen Failures	Text regarding individuals who do not meet the eGFR and NT-proBNP inclusion/exclusion criteria has been changed and shortened.	Clarification and simplification	Non-substantial
Section 6.1.1 Investigational Products Table 6	Added text on labelling of bottles for Part B.	Additional information to aid the conduction of the study.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 6.1.1 Investigational Products	Added text on taking study intervention.	Additional information to aid the conduction of the study.	Non-substantial
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Text regarding allocation of participants in Part B has been changed.	To reflect changes in study design for Part B.	Substantial
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	New text: A maximum of 25% of the participants can have 6MWD ≥ 350 and ≤400 meters at randomisation visit.	Clarification	Non-substantial
Section 6.5 Concomitant therapy	Silymarin has been added to the list of treatments that are prohibited and/or restricted.	Additional information to aid the conduction of the study.	Non-substantial
Section 6.5.1 Rescue Medicine	Section 6.5.1 has been removed. The text in this section has been added to section 8.2.5.	To improve readability of the document.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Added text (Pregnancy)	Clarification	Non-substantial
Section 7.2 Participant Withdrawal from the Study	Deleted text 'safety'	Clarification	Non-substantial
Section 8 Study Assessments and Procedures	Changed text regarding maximum amount of blood to be collected for Part B (approximately 300 mL).	Clarification	Non-substantial
Section 8.1.1 Patient Reported Outcomes	The text regarding the remote visits for Part B has been removed/edited.	To reflect changes in study design for Part B.	Substantial
Section 8.1.1 Patient Reported Outcomes	Added text (with the exception of the CCI [redacted] which is to be competed before the 6MWT).	Clarification	Non-substantial
Section 8.1.1 Patient Reported Outcomes	Added text for additional PROs to be used in Part B CCI [redacted].	To reflect changes in study design for Part B.	Substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 8.1.1.2 Patient Global Impression of Severity in Heart Failure Symptoms (Part A only)	Removed text ('Part A only', 'and is used to CCI [redacted]).	To reflect changes in study design for Part B.	Non-substantial
Section 8.1.1.3 Patient Global Impression of Severity in Walking Difficulties (Part A only)	Removed text ('Part A only', 'and will be used to CCI [redacted]	To reflect changes in study design for Part B.	Non-substantial
Section 8.1.4 Echocardiography	Heading changed to Echocardiogram. Subsections (8.1.4.1 and 8.1.4.2) created to present Part A-specific and Part-B-specific text separately Minor changes in Part A-specific section.	To align the terminology throughout the document. To reflect changes in study design for Part B.	Non-substantial
Section 8.2.1 Physical Examination	Text regarding full physical examinations for Part B has been edited.	To reflect changes in study design for Part B.	Non-substantial
Section 8.2.2 Vital signs	Subsection created for Part A-specific text (8.2.2.1). Removed text that is not applicable anymore.	To improve readibility	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 8	Edited text regarding centrally and locally performed analyses. Added footnote 'b' to Table 8.	Clarification	Non-substantial
Section 8.2.5 Skin Reactions, Including Maculopapular Rash	Text from the removed section 6.5.1 has been placed in 8.2.5.	To improve readability of the document.	Non-substantial
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Final follow up visit for Part B changed to Visit 8.	To reflect changes in study design for Part B.	Substantial
Section 8.3.9 Medication Error	New subsections with an additional text have been created (8.3.9.1 and 8.3.9.2).	To introduce revised language regarding Drug misuse/Drug	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
		abuse from the new CSP Template	
Section 8.5.1 Pharmacokinetics	Text regarding visits at which the last dose is taken in Part B has been changed.	To reflect changes in study design for Part B.	Substantial
Section 8.5.2. Pharmacodynamics	Text added regarding optinional NT-proBNP sampling.	To aid the enrolment of potential participants.	Non-substantial
Section 8.6.1 Collection of Blood Samples for MPO Quantification	Text removed (or serum)	To clarify that the measurement of MPO is to be performed exclusively in plasma.	Non-substantial
Section 8.6.2 Collection of Mandatory Samples for Exploratory Biomarker Analysis	Heading has been edited (added 'and Metabolite'). Text added regarding Part B.	To reflect changes in study design for Part B.	Non-substantial
Section 8.6.3 Collection of Mandatory Sample for Genetic Analysis	Text regarding sampling for Part B has been added.	To reflect changes in study design for Part B.	Non-substantial
Section 9 Statistical Considerations	Text regarding statistical consideration for Part B has been rewritten.	To reflect changes in study design for Part B.	Substantial
Appendix A1	Text regarding serious Breach has been introduced under heading 'Regulatory Reporting Requirements for Serious Breach'.	To introduce revised language from the new CSP Template	Non-substantial
Appendix A7	Retention of documents changed to '25 years'.	To reflect the change in regulatory requirements	Non-substantial
Appendix B4	Text regarding Drug Misuse/Drug Abuse has been introduced.	To introduce revised language regarding Drug Misuse/Drug Abuse from the new CSP Template	Non-substantial
Appendix O, COVID-19 Specifics	Text has been edited.	Clarification To reflect current recommendations regarding COVID-19.	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomised, Double-blind, Placebo-controlled, Multi-center Sequential Phase 2b and Phase 3 Study to Evaluate the Efficacy and Safety of AZD4831 Administered for Up to 48 Weeks in Participants with Heart Failure with Left Ventricular Ejection Fraction > 40%

Short Title: A Sequential Phase 2b and Phase 3 Study to Evaluate the Efficacy and Safety of AZD4831 in Participants with Heart Failure with Left Ventricular Ejection Fraction > 40%

Rationale: This study aims to evaluate the effect of AZD4831 on functional and symptomatic improvement in participants with heart failure with left ventricular ejection fraction > 40%. Additionally, the PK and overall safety profile of AZD4831 will be evaluated.

Objectives and Endpoints

Part A (Phase 2b)	
Objectives	**Endpoints/Variables**
Primary	
To evaluate the effect of AZD4831 on KCCQ-TSS	KCCQ-TSS change from baseline at 16 weeks compared with placebo
To evaluate the effect of AZD4831 on 6MWD	6MWD change from baseline at 16 weeks compared with placebo
Secondary	
To evaluate the effect of AZD4831 on KCCQ-TSS	KCCQ-TSS change from baseline at 24 and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on 6MWD	6MWD change from baseline at 24 and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on NT-proBNP	NT-proBNP change from baseline at 16, 24 and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LV-GLS	LV-GLS change from baseline at 16 and 24 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LAVI	LAVI change from baseline at 16 and 24 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LVMI	LVMI change from baseline at 16 and 24 weeks compared with placebo
To assess the pharmacokinetics of AZD4831	Concentrations will be summarised by timepoint and dose level.
To evaluate the effect of AZD4831 on inflammatory biomarkers	hsCRP and IL-6 change from baseline at 16, 24, and 48 weeks compared with placebo

Safety	
To assess the safety and tolerability of AZD4831 as compared with placebo in participants with HF	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG. Assessments related to AEs will cover: • Occurrence/Frequency • Seriousness • Death • AEs leading to discontinuation of IP • AEoSIs related to skin reactions, including maculopapular rash, and infection Vital signs parameters include blood pressure, pulse rate, and body temperature; assessments will cover: • Observed value • Absolute change from baseline values over time • Orthostatic blood pressure A complete list of laboratory parameters is presented in Section 8.2.4; assessments will cover: • Observed value • Absolute change from baseline values over time • Treatment-emergent changes in selected laboratory parameters Electrocardiogram measurements assessments will cover: • Investigator evaluation
Part B (Phase 3)	
Objectives	**Endpoints/Variables**
Primary	
To assess the effect of AZD4831 on heart failure symptoms	KCCQ-TSS, primary assessment at 24 weeks
To assess the effect of AZD4831 on functional capacity	6MWD, primary assessment at 24 weeks
Secondary	
To assess the effect of AZD4831 on diagnostic biomarkers	NT-proBNP, primary assessment at 24 weeks
To assess the effect of AZD4831 on inflammatory biomarkers	hsCRP and IL-6, primary assessment at 24 weeks

Safety	
To assess the safety and tolerability of AZD4831	• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of study intervention, possibly related AE as assessed by investigator, possibly related SAE as assessed by investigator. • Observed laboratory value, change from baseline and time to first treatment emergent abnormality. • Observed vital sign value, change from baseline, and time to first treatment emergent abnormality. • Observed ECG abnormalities, change from baseline, and time to first treatment emergent abnormality. • Occurrence and time to first occurrence of AEoSI categories: skin reactions, including maculopapular rash, and infection.

6MWD, 6-minute walk distance; AE, adverse event; AEoSI, adverse event of special interest; ECG, electrocardiogram; hsCRP, high-sensitivity C-reactive protein; KCCQ, Kansas City Cardiomyopathy Questionnaire; HF, heart failure; IL-6, interleukin 6; IP, Investigational Product; LAVI, left atrial volume index; LV-GLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; TSS, total symptom score.

For Tertiary/Exploratory objectives and endpoints descriptions, see Section 3 of the protocol.

Overall Design

This is a sequential, randomised, double-blind, placebo-controlled, multi-centre Phase 2b/3 study to evaluate the efficacy and safety of AZD4831 in participants with HF with LVEF > 40%. AZD4831 will be administered in addition to optimal background therapy for co-morbidities for 48 weeks (Part A), and 24, 36 or 48 weeks (Part B). In Phase 2b (Part A), approximately 660 participants will be randomised in 3 treatment groups in 1:1:1 allocaton, and will receive once-daily oral dose of either AZD4831 2.5 mg, AZD4831 5 mg, or placebo. In Phase 3 (Part B), approximately 820 participants will be randomised in 2 treatment groups in 1:1 allocation, and will receive once-daily oral dose of AZD4831 (either 2.5 mg or 5 mg based on interim results of Part A) or placebo. Randomisation in both phases will be stratified by neutrophil count.

Disclosure Statement: This is a double-blind (participant, investigator, and sponsor blinded) parallel group treatment study with 3 arms in Part A and 2 arms in Part B.

Number of Participants:

	Part A	Part B
Enrolled	Estimated 1100 participants	Estimated 1350 participants
Randomised	Estimated 660 participants	Estimated 820 participants
Participants with complete safety data	Estimated 600 participants	Estimated 745 participants

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are enrolled for the purpose of determining eligibility for the study, but are not randomised in the study, are considered "screen failures", unless otherwise specified by the protocol.

The study will be conducted in approximately 180 sites and approximately 15 countries.

Intervention Groups and Duration:

In Part A, participants will undergo a screening period of up to 4 weeks, followed by randomisation across 3 different treatment arms. Eligible participants will be randomised at a 1:1:1 ratio and dosed orally once daily. The planned treatment arms are AZD4831 2.5 mg, AZD4831 5 mg, and placebo. Participants will receive either AZD4831 or placebo for 16 weeks and then continue into a safety extension, during which they will receive an additional 32 weeks of the intervention (AZD4831 or placebo, as per their assigned arm during randomisation). A final follow-up visit (end of study visit) will occur at 52 weeks from randomisation. In the event that randomisation to the AZD4831 5 mg treatment arm is stopped during the study in either the whole study or in a country or specific ethnic population due to safety, the remaining participants in that cohort would be randomised at a 2:1 ratio to AZD4831 2.5 mg or matching placebo.

In Part B, participants will undergo a screening period of up to 2 weeks, followed by randomisation across 2 treatment arms. Eligible participants will be randomised at a 1:1 (AZD4831:placebo) ratio and dosed orally once daily. The planned treatment groups are AZD4831 at the dose selected based on Part A, and placebo. Participants will be treated for 24, 36 or 48 weeks, depending on when in time they were enrolled. The date of the last participant randomised in the study will determine the treatment period for patients who are still in the study. When the last patient is randomised, the end of the 24 week treatment period will be known; therefore the end of treatment date for all other ongoing participants will be scheduled in advance to occur at 24, 36 or 48 weeks. Consequently, earlier enrolment will allow a longer treatment period, whereas later enrolment will restrict the treatment period to 24 weeks. Participants will be treated for a minimum of 24 weeks to allow sufficient time for

efficacy evaluation, and a maximum of 48 weeks to assess longer-term safety and effect of the IP. A final end of study visit will occur 4 weeks after the final dose.

Participants can be randomised only once in the study; therefore, participants who were randomised into Part A cannot be included in Part B.

Data Monitoring Committee: Yes

Data Review Committee: For Part A, an unblinded DRC consisting of AZ personnel, an external dermatologist, and an external cardiologist will be set up for ongoing, periodic safety monitoring, with a focus on skin reactions. Additional details will be contained in the DRC charter.

Unblinded Review Committee: A URC consisting of a limited number of AZ personnel will be formed to review data from Part A from at least one, but possibly several, interim analyses, with the purpose of informing further development of the clinical programme, including but not limited to dose selection for Part B. The URC will review the risk/benefit profile and make recommendations on the dose for Part B and, based on safety, on the continuation of the program. When all participants in Part A have completed Week 52,the Part A data will be analysed as final interim analysis.

External Data Monitoring Committee: For Part B, an independent DMC, including a dermatologist, will be responsible for monitoring the safety of the study participants and making appropriate recommendations based on the available data. The DMC will have access to the unblinded data. The committee will operate in accordance with a DMC Charter.

Statistical Methods

The primary and key secondary endpoints (variables will be change from baseline) will be analysed using ANCOVA for Part A and Part B. The analyses will use baseline as covariate (for the relevant endpoint) and will be adjusted for the stratification factor for neutrophil count for Part A and Part B. In Part B, a treatment-by-baseline interaction term will be included as an independent variable in the model for KCCQ-TSS.

<u>Sample size estimation for Part A:</u>

Approximately 660 participants randomised, of which we estimate approximately 600 will have complete safety data, and 1:1:1 allocation is chosen to have enough participants exposed to AZD4831 at the therapeutic dose to fulfil the minimum requirement in the ICH E1 guideline on population exposure, taken together with Part B of this study, as well as a second function and symptom study with a similar design as Part B, and Phase 1 studies completed ahead of submission.

With 85% power at a significance level of $\alpha = 0.05$, 200 participants per arm (220 randomised) will allow detection of a difference of 6.0 points in mean change from

baseline between active and placebo in KCCQ-TSS comparing each active arm with placebo. The critical value for statistical significance is 3.9 points. The corresponding number for 6MWD is 21 meters and 14 meters. Calculations of detectable differences and critical values are based on ANCOVA, which will also be used for the analysis.

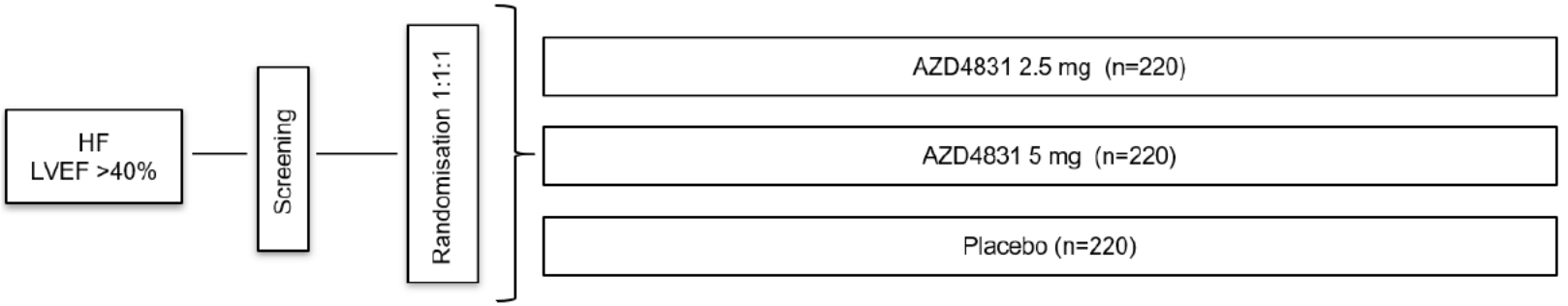
Sample size estimation for Part B:

Approximately 820 participants will be randomised in 1:1 allocation, of which we estimate approximately 745 will have complete safety data. The sample size is chosen to have enough participants exposed to AZD4831 at the therapeutic dose to fulfil the minimum requirement in the ICH E1 guideline on population exposure, taken together with Part A of this study as well as a second function and symptom study with a similar design as Part B, and Phase 1 studies completed ahead of submission.

The power to assess the two primary efficacy objectives will, given the assumed effect, exceed 90% at an alpha of 0.025.

1.2 Schema

Figure 1 Study Design – Part A



	S		R[a]	16w Treatment Period (Double-blind)					32w Safety Extension (Double-blind)			FUP
Visit	V1	V2 Remote	V3	V4	V5 Remote	V6	V7 Remote	V8	V9	V10	V11/EDV	V12
Week	Up to -4	-1	0	4	8	12	15	16	24	36	48	52
Day	Up to -28	-7	1	29	57	85	106	113	169	253	336	365
Measurements	KCCQ 6MWT Echo NT-ProBNP	KCCQ[b]	KCCQ 6MWT NT-ProBNP hsCRP and IL-6		AE	CCI	KCCQ[b]	KCCQ 6MWT Echo NT-ProBNP hsCRP and IL-6	KCCQ 6MWT Echo NT-ProBNP hsCRP and IL-6		KCCQ 6MWT NT-ProBNP hsCRP and IL-6	

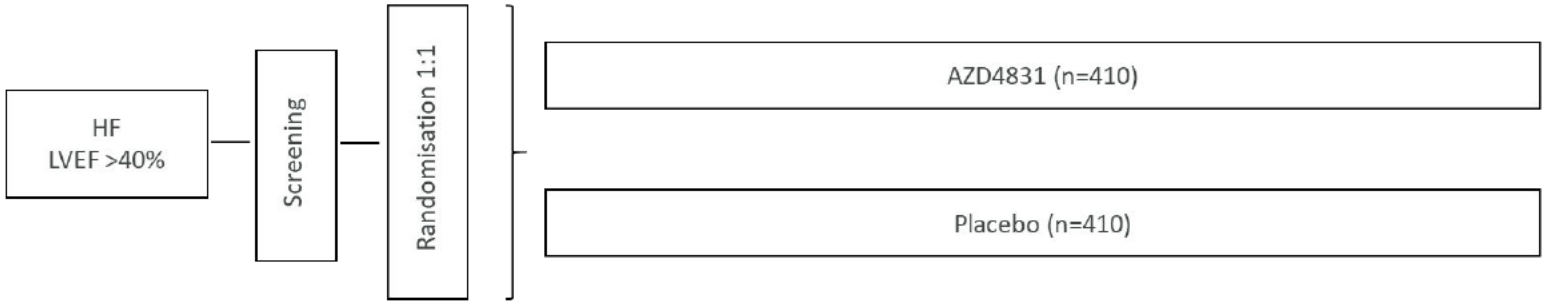
[a] Measurements/sampling performed before dosing
[b] To be completed by the participant at home on a provisioned tablet during 3 consecutive days on Week -1 and Week 15

Interim Analyses (Unblinded data review by an internal URC, including to start Part B)

Final Interim Analysis

6MWT, 6-minute walk test; AE, adverse event; Echo, echocardiogram; EDV, early discontinuation visit; FUP, follow-up; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal natriuretic peptide; R, randomisation; S, screening; URC, unblinded review committee; V, visit; w, week(s).

Figure 2 Study Design – Part B



	S	R[a]	Variable Treatment Period; 24w, 36w or 48w[b, c] (Double-blind)					EDV[d]	EoS[c, e]
Visit	V1	V2	V3	V4	V5	V6[f]	V7[g]	NA	V8
Week	-2 to 0	0	4	16	24	36	48	Variable	28/ 40/ 52
Day	-14 to 0	1	29	113	169	253	337	Variable	197/ 281/ 365
Measurements	KCCQ 6MWT NT-proBNP Echo[h]	KCCQ 6MWT NT-proBNP hsCRP and IL-6	PK[a]	KCCQ 6MWT NT-proBNP hsCRP and IL-6	KCCQ 6MWT NT-proBNP hsCRP and IL-6 CCI[a]	KCCQ 6MWT NT-proBNP hsCRP and IL-6	KCCQ 6MWT NT-proBNP hsCRP and IL-6	KCCQ 6MWT NT-proBNP hsCRP and IL-6	

[a] Measurements/sampling performed before dosing.
[b] Participants will be treated for 24, 36 or 48 weeks, depending on when in time they were randomised in the study.
[c] If study intervention is permanently discontinued, the participant should remain in the study, ie, continue to participate in scheduled study visits and evaluations.
[d] EDV will occur only for participants who are permanently discontinued from study intervention.
[e] EoS visit will take place 4 weeks after final dose, which may occur after 24, 36 or 48 weeks of treatment.
[f] V6 will occur only for participants treated for at least 36 weeks.

[g] V7 will occur only for participants treated for 48 weeks.
[h] Measurement not needed to be performed if historical Echo (<12m) is available.

6MWT, 6-minute walk test; EDV, early discontinuation visit; Echo, echocardiogram; EoS, End of Study; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NA, Not applicable; NT-proBNP, N-terminal natriuretic peptide; CCI [redacted], R, randomisation; S, screening; V, visit; w, week.

1.3 Schedule of Activities

Table 1 Schedule of Activities – Part A

Procedure	Screening		16-week treatment						32-week extension			Follow up	Details in CSP Section or Appendix
Visit	**1**	**2[a]**	**3[b]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11/EDV**	**12**	
Weeks from randomisation	**Up to -4**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**	**24**	**36**	**48**	**52**	
Study Day	**Up to -28**	**-7**	**1**	**29**	**57**	**85**	**106**	**113**	**169**	**253**	**336**	**365**	
Visit Window		**± 2 days**		**± 3 days**	**± 5 days**	**± 3 days**	**± 2 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Informed consent	X												Section 5.1
Informed consent for Genetic sampling (optional), future use blood and urine samples (optional)	X												Section 5.1
Inclusion and exclusion criteria	X		X										Sections 5.1 and 5.2
Medical history of alcohol, drugs of abuse, and nicotine use	X												
Demography	X												
Medical & surgical history	X												
Concomitant medication	X		X	X		X		X	X	X	X	X	Section 6.5
CCI [redacted]	[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		[redacted]		[redacted]
KCCQ [c]	X		X			X		X	X		X		Section 8.1.1.1
[redacted]			[redacted]			[redacted]		[redacted]					CCI [redacted]

Table 1 Schedule of Activities – Part A

Procedure	Screening		16-week treatment						32-week extension			Follow up	Details in CSP Section or Appendix
Visit	**1**	**2[a]**	**3[b]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11/EDV**	**12**	
Weeks from randomisation	**Up to -4**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**	**24**	**36**	**48**	**52**	
Study Day	**Up to -28**	**-7**	**1**	**29**	**57**	**85**	**106**	**113**	**169**	**253**	**336**	**365**	
Visit Window		**± 2 days**		**± 3 days**	**± 5 days**	**± 3 days**	**± 2 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
[redacted]			[redacted]			[redacted]		[redacted]					CCI [redacted]
[redacted]		[redacted]					[redacted]						CCI [redacted]
Full physical examination	X							X			X		Section 8.2.1
Skin examination			X	X		X			X	X		X	Section 8.2.1
Height	X												Section 8.2.1
Weight	X		X					X			X		Section 8.2.1
Vital signs [d]	X		X	X		X		X	X	X	X	X	Section 8.2.2
Orthostatic Test [e]			X			X							Section 8.2.2
12-lead ECG	X		X	X		X		X			X	X	Section 8.2.3
6MWT [f]	CCI [redacted]												Section 8.1.3

Table 1 Schedule of Activities – Part A

Procedure	Screening		16-week treatment						32-week extension			Follow up	Details in CSP Section or Appendix
Visit	**1**	**2[a]**	**3[b]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11/EDV**	**12**	
Weeks from randomisation	**Up to -4**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**	**24**	**36**	**48**	**52**	
Study Day	**Up to -28**	**-7**	**1**	**29**	**57**	**85**	**106**	**113**	**169**	**253**	**336**	**365**	
Visit Window		**± 2 days**		**± 3 days**	**± 5 days**	**± 3 days**	**± 2 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Urinalysis	X		X					X	X		X	X	Sections 8.2.4 and 8.6.2
FSH (females only)	X												Section 8.2.4
Clinical safety laboratory assessments	X		X	X		X		X	X	X	X	X	Section 8.2.4
ANCA testing			X								X		Section 8.2.4
NT-proBNP	CCI [redacted]												Section 8.5.2.1
PK blood sampling for AZD4831 [g]			X	X		X		X	X		X	X	Section 8.5.1
hsCRP and IL-6	CCI [redacted]												Section 8.5.2.1
Blood sample for MPO Quantification	X		X					X			X		Section 8.6.1
Blood sample for genetic analysis			X										Section 8.6.3
CCI [redacted]			[redacted]					[redacted]			[redacted]		[redacted]

Table 1 Schedule of Activities – Part A

Procedure	Screening		16-week treatment						32-week extension			Follow up	Details in CSP Section or Appendix
Visit	**1**	**2[a]**	**3[b]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11/EDV**	**12**	
Weeks from randomisation	**Up to -4**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**	**24**	**36**	**48**	**52**	
Study Day	**Up to -28**	**-7**	**1**	**29**	**57**	**85**	**106**	**113**	**169**	**253**	**336**	**365**	
Visit Window		**± 2 days**		**± 3 days**	**± 5 days**	**± 3 days**	**± 2 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
CCI [redacted]			[redacted]					[redacted]			[redacted]		[redacted]
CCI [redacted]			[redacted]					[redacted]			[redacted]		[redacted]
[redacted]				[redacted]							CCI [redacted]		[redacted]
Blood sample for potential diagnostic assay development	X		X										Section 8.6.4
Echocardiography [k]	X							X	X				Section 8.1.4
Randomisation			X										Section 6.3
Optional genomics initiative exploratory genetic sample			X										Section 8.7 and Appendix D
Optional future use blood and urine samples			X					X			X		Section 8.6.5
Study intervention dispensed (daily dosing [l])			X	X		X		X	X	X			Section 6.2
Study intervention return and accountability check				X		X		X	X	X	X		Sections 6.2 and 6.4

Table 1 Schedule of Activities – Part A

Procedure	Screening		16-week treatment						32-week extension			Follow up	Details in CSP Section or Appendix
Visit	**1**	**2[a]**	**3[b]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11/EDV**	**12**	
Weeks from randomisation	**Up to -4**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**	**24**	**36**	**48**	**52**	
Study Day	**Up to -28**	**-7**	**1**	**29**	**57**	**85**	**106**	**113**	**169**	**253**	**336**	**365**	
Visit Window		**± 2 days**		**± 3 days**	**± 5 days**	**± 3 days**	**± 2 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	
Assessment of AEs and SAEs [m]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of CV events			X	X		X		X	X	X	X	X	Section 8.1.5
Optional Study participant feedback questionnaire				X					X			X	Section 8.1.6

[a] Remote completion of KCCQ at Visit 2 and Visit 7 by participant (and telephone contact by the site to remind the participant of the first completion) and telephone contact by site with participant at Visit 5.
[b] Assessments and blood draws taken pre-dose at Visit 3.
[c] To avoid bias in participant responses, KCCQ will be completed prior to any other study procedures, following informed consent. KCCQ will also be completed by the participant at home on a provisioned tablet during 3 consecutive days on Week -1 and Week 15.
[d] Vital Signs: supine BP (average of 3 measurements), pulse rate, and body temperature will be measured.
[e] Orthostatic BP will be measured at baseline visit and at Visit 6 (Week 12) prior to any required blood draw and study intervention. Orthostatic BP will be measured 1 and 3 minutes after the participant stands.
[f] The 6MWT consists of a suite of assessments that are carried out before and after the 6MWT itself: CCI [redacted]
[g] One PK sample will be collected pre-dose from all participants. In a subset of participants (approximately 20%), 3 additional post-dose samples will be collected at Visit 6. Visit 6 sample collection times are: pre-dose, and 0.5 to 1.5 h, 1.5 to 3 h and > 3 h post-dose, with a minimum of 1 hour between the post-dose sampling occasions. Once approximately 20% of participants have been tested, no further participants would need this additional post dose sampling. For participants who are discontinued from investigational product due to rash, a PK sample should be collected at the discontinuation visit.
[h] CCI [redacted]
[i] CCI [redacted]
[j] Only for participants who discontinue investigational product due to rash or skin reaction: blood and urine sample for exploratory metabolite analysis should also be collected at the EDV.
[k] Screening echocardiogram can be performed on a different day if it is not possible to be done on the screening visit day due to scheduling purposes but must be as soon after the screening visit as possible ie, within 1-2 days in order to allow for results to be back prior to randomisation. For the echocardiogram at Visit 8 and Visit 9, if due to scheduling purposes the echocardiogram cannot be performed on the same day as the clinic visit, the echocardiogram should be performed at the earliest opportunity and within 7 days of the scheduled visit.
[l] The first dose of study intervention will be administered in clinic on the day of randomisation after completing all pre-dose procedures. Participants will receive study intervention at the site on visit days and at home between visits for a total of 48 weeks.
[m] AEs will be collected from the first dose (the only exception is related to the pre-dose orthostatic test at Visit 3: if orthostatic hypotension is confirmed, it should be reported as an AE, and symptoms related to the measurement of orthostatic vitals if present should also be reported as an AE). SAEs will be collected from signing of the ICF.

6MWT, 6-minute walk test; AEs, adverse events; ANCA, anti-neutrophil cytoplasmic antibodies; BP, blood pressure; CSP, clinical study protocol; ECG, electrocardiogram; EDV, early discontinuation visit; EoS, End of Study; FSH, follicle stimulating hormone; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; ICF, informed consent form; IL-6, interleukin 6; KCCQ, Kansas City Cardiomyopathy Questionnaire; MPO, myeloperoxidase; NT-proBNP, N-terminal pro-brain natriuretic peptide; CCI [redacted]
PK, pharmacokinetics; CCI [redacted]; SAE, serious adverse event; UACR, urinary albumin-to-creatinine ratio; CCI [redacted].

Table 2 Schedule of Activities – Part B

Procedure	S	R	Variable Treatment Period; 24, 36 or 48 weeks[a, b]					EDV[c]	EoS visit[b, d]	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6[e]**	**7[f]**	**NA**	**8**	
Weeks from randomisation	**-2 to 0**	**0**	**4**	**16**	**24**	**36**	**48**	**Variable**	**28/40/52**	
Study Day	**-14 to 0**	**1**	**29**	**113**	**169**	**253**	**337**	**Variable**	**197/281/365**	
Visit window		**Within 14 days from enrolment**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**		**± 7 days**	
Informed consent	X									Section 5.1
Enrolment in IRT/RTSM	X									Section 6.3
Randomisation		X								Section 6.3
Informed consent for genetic sampling (optional) and future use blood and urine samples (optional)	X									Section 5.1
Inclusion and exclusion criteria	X	X								Sections 5.1 and 5.2
Medical history of alcohol, drugs of abuse and nicotine use	X									
Demography	X									
Medical & surgical history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	Section 6.5
CCI [redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Table 2 Schedule of Activities – Part B

Procedure	S	R	Variable Treatment Period; 24, 36 or 48 weeks[a, b]					EDV[c]	EoS visit[b, d]	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6[e]**	**7[f]**	**NA**	**8**	
Weeks from randomisation	**-2 to 0**	**0**	**4**	**16**	**24**	**36**	**48**	**Variable**	**28/40/52**	
Study Day	**-14 to 0**	**1**	**29**	**113**	**169**	**253**	**337**	**Variable**	**197/281/365**	
Visit window		**Within 14 days from enrolment**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**		**± 7 days**	
KCCQ [g]	X	X		X	X	X	X	X		Section 8.1.1.1
PGIS-HF	X	X		X	X	X	X	X		Section 8.1.1.2
PGIS-WD	X	X		X	X	X	X	X		Section 8.1.1.3
CCI [redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Physical examination [h]	X	X	X	X	X	X	X	X	X	Section 8.2.1
Height	X									Section 8.2.1
Weight	X	X	X	X	X	X	X	X	X	Section 8.2.1
Vital signs [i]	X	X	X	X	X	X	X	X	X	Section 8.2.2
12-lead ECG	X	X	X		X		X	X	X	Section 8.2.3
Urinalysis	X	X		X	X	X	X	X	X	Section 8.2.4
FSH (females only)	X									Section 8.2.4
Clinical safety laboratory assessments	X	X	X	X	X	X	X	X	X	Section 8.2.4
ANCA testing		X								Section 8.2.4
CCI [redacted]			[redacted]		[redacted]					[redacted]

Table 2 Schedule of Activities – Part B

Procedure	S	R	Variable Treatment Period; 24, 36 or 48 weeks[a, b]					EDV[c]	EoS visit[b, d]	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6[e]**	**7[f]**	**NA**	**8**	
Weeks from randomisation	**-2 to 0**	**0**	**4**	**16**	**24**	**36**	**48**	**Variable**	**28/40/52**	
Study Day	**-14 to 0**	**1**	**29**	**113**	**169**	**253**	**337**	**Variable**	**197/281/365**	
Visit window		**Within 14 days from enrolment**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**		**± 7 days**	
NT-proBNP [j]	X	X		X	X	X	X	X		Section 8.5.2.1
Blood sample for genetic analysis		X								Section 8.6.3
hsCRP and IL-6		X		X	X	X	X	X		Section 8.5.2.1
CCI [redacted]		[redacted]								[redacted]
6MWT[k]	X	X		X	X	X	X	X		Section 8.1.3
Echocardiogram [l]	X									Section 8.1.4
CCI [redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]								[redacted]		[redacted]
Blood sample for potential diagnostic assay development	X	X								Section 8.6.4
Optional future use blood and urine sampling		X			X					Section 8.6.5

Table 2 Schedule of Activities – Part B

Procedure	S	R	Variable Treatment Period; 24, 36 or 48 weeks[a, b]					EDV[c]	EoS visit[b, d]	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6[e]**	**7[f]**	**NA**	**8**	
Weeks from randomisation	**-2 to 0**	**0**	**4**	**16**	**24**	**36**	**48**	**Variable**	**28/40/52**	
Study Day	**-14 to 0**	**1**	**29**	**113**	**169**	**253**	**337**	**Variable**	**197/281/365**	
Visit window		**Within 14 days from enrolment**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**		**± 7 days**	
Optional genomics initiative, exploratory genetic sample		X								Section 8.7 and Appendix D
Study intervention dispensed (daily dosing [n])		X	X	X	X	X				Section 6.2
Study intervention return and accountability check			X	X	X	X	X	X		Sections 6.2 and 6.4
Assessment of AEs and SAEs [o]	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of CV events			X	X	X	X	X	X	X	Section 8.1.5

[a] Participants will be treated for 24, 36 or 48 weeks, depending on when in time they were randomised in the study.
[b] If study intervention is permanently discontinued, the participant should remain in the study, ie, continue to participate in scheduled study visits and evaluations.
[c] EDV will occur only for patients who are permanently discontinued from study intervention.
[d] EoS visit will take place 4 weeks after final dose, which may occur after 24, 36 or 48 weeks of treatment. For participants who are discontinued from the study intervention, and later decide to withdraw from the study before scheduled EoS visit, the EoS visit should be performed at the time of withdrawal.
[e] V6 will occur only for participants treated for at least 36 weeks.
[f] V7 will occur only for participants treated for 48 weeks.
[g] To avoid bias in participant responses, KCCQ will be completed prior to any other study procedures, following informed consent.
[h] At Visits 1 and EoS/EDV, a full physical examination is performed.

[i] Vital Signs: supine BP (average of 3 measurements), pulse rate, and body temperature will be measured.
[j] An additional, local NT-proBNP test can be performed as pre-screening at the site. Participants must sign the specific Pre-Screening Informed Consent before collection of a blood sample for this procedure. This test can be done within 30 days preceding the Screening (Visit 1), and latest on the day of the Screening (Visit 1). The central lab result will be used to determine if the participant is eligible for the study.
[k] CCI [redacted]
[l] Screening echocardiogram can be performed on a different day if it is not possible to be done on the screening visit day due to scheduling purposes but must be performed as soon after the screening visit as possible in order to allow for results to be available prior to randomisation. Screening echocardiogram is not needed if there is an available echocardiogram performed up to 12 months before screening.
[m] To be sampled at Visit 2 and either Visit 5, Visit 6 or Visit 7, for participants treated for either 24, 36 or 48 weeks, resepectively.
[n] The first dose of study intervention will be administered in clinic on the day of randomisation after completing all pre-dose procedures. Participants will receive study intervention at the site on visit days and at home between visits for a total of 24, 36 or 48 weeks
[o] AEs will be collected from the first dose. SAEs will be collected from signing of the ICF

6MWT, 6-minute walk test; AEs, adverse events; ANCA, anti-neutrophil cytoplasmic antibodies; BP, blood pressure; CSP, clinical study protocol; ECG, electrocardiogram; EDV, early discontinuation visit; EoS, End of Study; FSH, follicle stimulating hormone; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; ICF, informed consent form; IL-6, interleukin 6; KCCQ, Kansas City Cardiomyopathy Questionnaire; MPO, myeloperoxidase; NT-proBNP, N-terminal pro-brain natriuretic peptide; CCI [redacted]; CCI [redacted]; PK, pharmacokinetics; CCI [redacted]; R, randomisation; S, screening; SAE, serious adverse event; UACR, urinary albumin-to-creatinine ratio; CCI [redacted].

2 INTRODUCTION

AZD4831 is a highly potent MPOi that is being developed for the management of cardiovascular disease, engaging both macro- and microvascular structure and function.

2.1 Study Rationale

This study aims to evaluate the effect of AZD4831 on functional improvement and reduction of symptoms in participants with heart failure with left ventricular ejection fraction > 40%. Additionally, the PK and overall safety profile of AZD4831 will be evaluated.

2.2 Background

Chronic HF continues to be a major cause of mortality, hospitalisations, and suboptimal quality of life. Even with the best possible treatment, the 5-year survival rate for HF patients is worse than for most cancers (Braunwald 2015). Heart failure affects 2% of the Western population, increases to 10% over the age of 65 years, and up to 20% over the age of 75 years (Go et al 2014). The proportion of the Western population over the age of 65 years is expected to increase to over 30% by year 2050 and the costs of HF to society are expected to triple between years 2010 and 2030. Heart failure is currently broadly divided into three categories based on the systolic function of the left ventricle: (1) HFrEF (LVEF < 40%), (2) HFmrEF (LVEF 40-49%), and (3) HFpEF (LVEF ≥ 50%). Together, HFmrEF and HFpEF account for 55% of HF cases; HFpEF and HFrEF are distinct clinical phenotypes with differing underlying pathophysiology, while HFmrEF appears to share some features of both HFrEF and HFpEF whilst remaining a possible independent category. Over recent years, there has been a drive to include HFmrEF patients into future HF studies in order to learn more about this category while evaluating new therapies for the treatment of either HFpEF or HFrEF. To further increase knowledge about this condition, patients with HFmrEF will be included in the current study.

Heart failure with preserved ejection fraction is overrepresented in elderly and in women. Mortality in the community approaches 25% at one year. In a comparison of trial populations, the prognosis in HFpEF is 50-75 deaths and 40-75 HF hospitalisations per 1000 patient-years, whereas in stable coronary disease it is 10-30 deaths and 5-10 hospitalisations per 1000 patient-years and has improved further with modern therapy. Thus, novel interventions for coronary artery disease have little potential, whereas for HFpEF, novel treatment is both a critical unmet need and of great public health impact, if successful (Butler et al 2014, McMurray et al 2012).

A novel paradigm for HFpEF pathophysiology states that co-morbidities (renal disease, hypertension, obesity, and diabetes) lead to a global inflammatory state, leading to immune cell recruitment and endothelial and coronary microvascular dysfunction, with distinct

pathophysiology different from macrovascular coronary disease (Paulus and Tschope 2013). This, in turn, can lead to both extracellular fibrosis and myocardial stiffness and reduced myocardial nitric oxide bioavailability and cyclic guanosine monophosphate content and impaired myocyte relaxation. Numerous clinical data support this hypothesis.

Coronary endothelial dysfunction is associated with diastolic dysfunction and with worse outcomes in HFpEF. Exercise studies implicate vascular stiffness and impaired exercise vasodilation and suggest that impaired diastolic reserve may be related to endothelial and microvascular dysfunction. Angina and false positive stress tests are common in HFpEF. Further, recent autopsy studies have provided convincing evidence of coronary microvascular rarefaction in HFpEF (Mohammed et al 2015). Using transthoracic Doppler echocardiography - coronary flow velocity reserve approach, Shah et al (2018) was the first to provide robust evidence that coronary microvascular dysfunction is highly prevalent in HFpEF, as diagnosed according to guidelines.

Myeloperoxidase is a highly abundant protein mainly present in azurophilic granules of neutrophils, constituting 5% of the dry weight of the cells. In addition to neutrophils, there are also data suggesting the presence of MPO in monocytes and macrophages. MPO can be secreted, and is unique in its ability to generate reactive chlorinating species such as hypochlorous acid, the active component of bleach, which possesses potent bactericidal and viricidal activities. In addition, hypochlorous acid reacts with electron-rich moieties of a large range of biomolecules (Nicholls and Hazen 2005).

Multiple lines of evidence suggest that MPO may play a role in atherogenesis in humans (Baldus et al 2003, Brennan et al 2003, Zhang et al 2001) and MPO plasma levels predict outcome of cardiovascular disease. In chronic HF, plasma levels of MPO are elevated and also associated with more advanced HF (Tang et al 2006). Additionally, elevated plasma MPO levels can predict increased adverse clinical outcomes in HF patients (Tang et al 2007). Individuals with inherited low MPO activity were protected from leukocyte activation induced deterioration of vascular function (Rudolph et al 2012). Direct MPO administration in anaesthetised pigs increased the tone of conductance and resistance vessels and adversely affected myocardial blood flow, thereby strengthening the concept that MPO indeed acts as a modulator of vascular tone in vivo and identifying MPO as a systemic regulator of vasomotion in humans and thus a potential therapeutic target (Rudolph et al 2012). MPO is also involved in structural remodelling of the myocardium, leading to an increased vulnerability to atrial fibrillation (Rudolph et al 2010).

Overall, recent evidence suggests that MPO may provide a mechanistic link between inflammation, oxidative stress, vascular dysfunction and impaired cardiac remodelling. It is thus hypothesised that the MPO inhibitor AZD4831 will improve coronary microvascular

status as well as systemic endothelial function, leading to improved diastolic function and overall status of HFpEF patients.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD4831 is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

Potential risks of AZD4831 and mitigation strategy are shown in Table 3. More detailed information about the known and expected benefits and potential risks of AZD4831 may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

All study activities are considered routine clinical practice and judged not to expose participants to any additional risks.

Table 3 Risk Assessment

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
AZD4831		
Maculopapular rash	Generalized maculopapular rash has been observed in healthy volunteers in completed global SAD/MAD studies at single doses of 45 mg and above and at repeated doses of 15 mg and above, at 7-10 days post dose. In the Phase IIa study in participants with HFpEF, 1 of 27 participants had generalized maculopapular rash CTCAE Grade 3 at AZD4831 5 mg occurring 5 days after up-titration from 2.5 to 5 mg. In a single-blind multiple-ascending dose study in healthy Japanese and Chinese participants, maculopapular rash CTCAE Grade 1 was reported in 1 of 6 Japanese participants on AZD4831 5 mg, and maculopapular rash Grade 2 was reported in 1 of 6 Chinese participants on AZD4831 5 mg and in 3 of 6 Japanese participants on AZD4831 10 mg. See IB Section 6.3 for further information.	Exclusion criteria 5. Specific discontinuation criteria. AEoSI with special data collection/eCRF. DRC oversight in Part A and DMC in Part B, both including dermatologist representation. Protocol measures for Part A to stop randomisation to the AZD4831 5 mg treatment arm or in specific countries or ethnic populations in response to emerging safety information. Dose selection for Part B.

Table 3 Risk Assessment

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
AZD4831		
Host-defence impairment (infections, including pneumonia)	The MPO in neutrophils generate ROS to fight infecting microorganisms; therefore, there is a theoretical risk that treatment with an MPO inhibitor could impair host-defence mechanisms. Humans with total or partial MPO deficiency generally do not have an increased susceptibility to infections but the incidence of Candida infections may be increased. An increased incidence of infection has not been seen in participants in clinical studies with AZD4831. See IB Section 6.2 for further information.	AEoSI. AE monitoring for infections and relevant labs (CBC, hsCRP).
CCI	In the nonclinical safety studies in rats and dogs, inhibition of CCI caused reversible CCI . These effects have also been observed in nonclinical and clinical studies with other compounds of the same class and the magnitude of this effect is related to the degree of selectivity CCI . Clinically relevant changes in CCI have not been seen in limited clinical data with AZD4831. See IB Section 6.2 for further information.	Monitoring CCI . Specific discontinuation criteria.
CCI	There is a CCI in the AZD4831 molecule, since it is known that CCI . In completed nonclinical studies CCI has not been seen in participants in clinical studies with AZD4831. See IB Section 6.2 for further information.	Monitoring WBC differential
CCI reduction and CCI increase	In secondary pharmacology studies, AZD4831 was shown to be an inhibitor of CCI . Inhibition of this receptor is known to decrease CCI . Clinically relevant changes in CCI have not been seen in participants in clinical studies with AZD4831. See IB Section 6.2 for further information.	Monitoring CCI

Table 3 Risk Assessment

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
AZD4831		
Anaemia and inflammation	One high-dose CCI dog developed severe clinical symptoms on CCI of dosing and did not recover sufficiently to allow further dosing. The dog was euthanised on CCI showed CCI ation. The cause of these findings is unknown. No other dogs in any studies with AZD4831 showed similar symptoms or CCI . Clinically relevant CCI have not been seen in participants in clinical studies with AZD4831. See IB Section 6.2 for further information.	Routine CCI monitoring.
CCI	CCI has been shown in transgenic CCI mice in the CCI dose range finding study. CCI findings included increased CCI . Pathology showed CCI , increased CCI showed CCI No CCI were observed at CCI Clinically relevant changes in kidney function have not been seen in participants in clinical studies with AZD4831. See IB Section 6.2 for further information.	Exclusion criterion of eGFR < 30mL/min/1.73m2 (See exclusion criterion 1). Routine monitoring of renal function (creatinine)
Other		
COVID-19 pandemic risks	While there is a theoretical risk that treatment with an MPO inhibitor could impair host-defence mechanisms, an increased incidence of infection with SARS-CoV-2 has not been seen in limited clinical data with AZD4831; therefore, the risk to participants exposed to SARS-CoV-2 or to those who suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular HF. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).	Participants with signs or confirmation of infection may be excluded from the study (See exclusion criterion 23). Further risk mitigation measures are detailed in Appendix O

Table 3 Risk Assessment

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy

AEoSI, adverse event of special interest; BP, blood pressure; CBC complete blood count; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; DMC, Data Monitoring Committee; DRC, Data Review Committee; eCRF, electronic case report form; HF, heart failure; CCI ; HR, heart rate; hsCRP, high-sensitivity C-reactive protein; IB, Investigator's Brochure; MPO, myeloperoxidase; CCI ; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T3, triiodothyronine; T4, thyroxine; CCI ; WHO, World Health Organisation.

2.3.2 Benefit Assessment

All participants in the study are expected to be optimally treated according to local guidelines, including treatments to control co-morbidities, and the study intervention may be used in conjunction with standard of care for any comorbidities. Participants involved in the proposed study may benefit from the given treatment.

All participants of clinical trials irrespective of whether treated with active treatment or not, generally receive closer medical attention than those in ordinary clinical practice which may be to their advantage.

Heart failure with LVEF > 40% is a common condition with rising prevalence associated with poor quality of life and adverse prognosis for which there are no approved therapies; therefore, information acquired from this study could be of benefit to patients in the future.

2.3.3 Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with AZD4831 are justified by the anticipated benefits that may be afforded to participants with HF with LVEF > 40%.

3 OBJECTIVES AND ENDPOINTS

3.1 Part A

The following information in Table 4 relates to the objectives of Part A of the study. The dose in Part B will be the dose with optimal risk-benefit profile based on the data in Part A.

Table 4 Objectives and Endpoints – Part A

Objectives	Endpoints/Variables
Primary	
To evaluate the effect of AZD4831 on KCCQ-TSS	KCCQ-TSS change from baseline at 16 weeks compared with placebo
To evaluate the effect of AZD4831 on 6MWD	6MWD change from baseline at 16 weeks compared with placebo
Secondary	
To evaluate the effect of AZD4831 on KCCQ-TSS	KCCQ-TSS change from baseline at 24 and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on 6MWD	6MWD change from baseline at 24 and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on NT-proBNP	NT-proBNP change from baseline at 16, 24, and 48 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LV-GLS	LV-GLS change from baseline at 16 and 24 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LAVI	LAVI change from baseline at 16 and 24 weeks compared with placebo
To evaluate the effect of AZD4831 on echocardiographic parameter LVMI	LVMI change from baseline at 16 and 24 weeks compared with placebo
To assess the pharmacokinetics of AZD4831	Concentrations will be summarised by timepoint and dose level
To evaluate the effect of AZD4831 on inflammatory biomarkers	hsCRP and IL-6 change from baseline at 16, 24, and 48 weeks compared with placebo

Table 4 Objectives and Endpoints – Part A

Objectives	Endpoints/Variables
Safety	
To assess the safety and tolerability of AZD4831 as compared with placebo in participants with HF	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG. Assessments related to AEs will cover: • Occurrence/Frequency • Seriousness • Death • AEs leading to discontinuation of IMP • AEoSIs related to skin reactions, including maculopapular rash, and infection Vital signs parameters include blood pressure, pulse rate, and body temperature; assessments will cover: • Observed value • Absolute change from baseline values over time • Orthostatic blood pressure A complete list of laboratory parameters is presented in Section 8.2.4; assessments will cover: • Observed value • Absolute change from baseline values over time • Treatment-emergent changes in selected laboratory parameters Electrocardiogram measurements assessments will cover: • Investigator evaluation
Tertiary/Exploratory	
CCI [redacted]	[redacted]

Table 4 Objectives and Endpoints – Part A

Objectives	Endpoints/Variables
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
To evaluate the effect of AZD4831 on CV events	Composite of HF hospitalisation, urgent HF visits with requirement for additional loop diuretic treatment, MI, CV deaths, and all-cause mortality from baseline to end of study
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 Objectives and Endpoints – Part A

Objectives	Endpoints/Variables
CCI [redacted]	

3.2 Part B

The following information in Table 5 relates to the objectives of Part B of the study.

Table 5 Objectives and Endpoints – Part B

Objectives	Endpoints/Variables
Primary	
To assess the effect of AZD4831 on heart failure symptoms	KCCQ-TSS, primary assessment at 24 weeks
To assess the effect of AZD4831 on functional capacity	6MWD, primary assessment at 24 weeks
Secondary	
To assess the effect of AZD4831 on diagnostic biomarkers	NT-proBNP, primary assessment at 24 weeks
To assess the effect of AZD4831 on inflammatory biomarkers	hsCRP and IL-6, primary assessment at 24 weeks

Table 5 Objectives and Endpoints – Part B

Objectives	Endpoints/Variables
Safety	
To assess the safety and tolerability of AZD4831	• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of study intervention, possibly related AE as assessed by investigator, possibly related SAE as assessed by investigator. • Observed laboratory value, change from baseline and time to first treatment emergent abnormality. • Observed vital sign value, change from baseline, and time to first treatment emergent abnormality. • Observed ECG abnormalities, change from baseline, and time to first treatment emergent abnormality. • Occurrence and time to first occurrence of AEoSI categories: skin reactions, including maculopapular rash, and infection.
Tertiary	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomised, double-blind, placebo-controlled, multi-centre sequential Phase 2b and Phase 3 study to evaluate the efficacy and safety of AZD4831 in participants with HF with LVEF > 40%. The study will consist of 2 separate parts; see the study flow charts in Figure 1 and Figure 2.

Part A will evaluate the efficacy and safety of once-daily oral dosing of AZD4831 2.5 mg or 5 mg compared to placebo, administered in addition to optimal background therapy for co-morbidities for 16 weeks in participants with HF with LVEF > 40%. Approximately 660 participants will be randomised in a 1:1:1 allocation, of which we estimate approximately 600 will have complete safety data to establish efficacy as well as the safety and tolerability profile, and identify and select a dose for the pivotal part of the study (Part B). Randomisation will be stratified by neutrophil count. Participants in Part A will continue into a safety extension, during which they will receive an additional 32 weeks of the intervention (AZD4831 or placebo, as per their assigned arm during randomisation). The primary and secondary endpoints will be evaluated at 16, 24, and 48 weeks (echocardiography parameters will be evaluated at 16 and 24 weeks only).

An unblinded review will be performed of at least one, but possibly several, interim analyses by an internal Unblinded Review Committee, with the purpose of informing further development of the clinical programme, including but not limited to dose selection to start Part B. One of the interim analyses will be performed when all participants in Part A have completed the last protocol-specified visit/assessment. If Part B were not to start or progress, then the last interim analysis of Part A would be regarded as the final analysis.

Part B will evaluate the efficacy and safety of once-daily oral dosing of AZD4831, administered in addition to optimal background therapy for co-morbidities for 24, 36 or 48 weeks to a new cohort of participants with HF with LVEF > 40%. Approximately 820 participants will be randomised, of which we estimate approximately 745 will have complete safety data. Analysis of Part B will be based on participants in Part B only. Randomisation will be stratified by neutrophil count. Participants will receive once-daily oral doses of the selected dose of AZD4831 or placebo in a 1:1 allocation. The primary and secondary endpoints will be evaluated at 24 weeks.

The efficacy, safety, and tolerability data from Part A will be evaluated by an internal URC at at least one, but possibly several, interim analyses (see Appendix A 5). Based on this data, the dose for Part B of the study will be selected. The analysis of Part A will be performed by study-independent sponsor personnel.

Oversight from an unblinded DRC focusing on skin reactions for part A and external DMC for part B will be included for this study; see Appendix A 5 for more details.

4.2 Scientific Rationale for Study Design

This is a randomised, multi-centre, double-blind, placebo-controlled study. Randomisation and double-blinding will minimise potential bias. The target population includes both male and female participants aged ≥ 40 years with an established diagnosis of HF with LVEF > 40% and evidence of structural heart disease (ie, left ventricular hypertrophy or left atrial enlargement). Detailed characteristics of the target population can be seen in inclusion criteria (see Section 5.1). These requirements in combination with elevated natriuretic peptides aims to support the diagnosis of HF, since other common co-morbidities may cause overlapping symptoms.

The control group will receive matching placebo; there are no approved pharmacological treatments for HF with LVEF > 40% that could be used as a comparator. All participants will be treated according to local guidelines on standard of care treatment, focusing on treatment of HF symptoms (eg, diuretics) and co-morbidities (including treatment for hypertension, ischaemic heart disease, and atrial fibrillation/flutter).

The study is designed to evaluate the efficacy and safety of AZD4831 in HF subjects with LVEF > 40% and is made up of 2 separate parts: Part A is intended to establish efficacy as well as the safety and tolerability profile of AZD4831 and identify and select a dose for the pivotal study Part B. Part B is intended to confirm the efficacy and safety of the selected dose.

The primary endpoints in Part A are change from baseline in KCCQ-TSS and 6MWD at 16 weeks compared with placebo. The primary endpoints in Part B are change from baseline in KCCQ-TSS and 6MWD at 24 weeks compared with placebo.

The rationale for using change in 6MWD is that the 6MWT (the test used to determine the 6MWD) can act as a surrogate of normal daily activity. The 6MWT is a standard method for measuring exercise response (American Thoracic Society 2002, Holland et al 2014) to medical interventions in patients with moderate to severe heart or lung disease, having already been used to give pre-treatment and post-treatment comparisons for patients with HF (De Bock et al 1994, O'Keeffe et al 1998).

Patients with HF experience debilitating symptoms that substantially impact daily functioning, physical capacity, and quality of life. For these reasons, it is important to measure the impact of new HF therapies on the HF patients' symptoms and functioning (Zannad et al 2013). The KCCQ instrument quantifies both the frequency of four cardinal HF-symptoms (fatigue, peripheral oedema, dyspnoea, and orthopnoea) and how bothersome three of the cardinal HF-symptoms (fatigue, peripheral oedema and dyspnoea) are to patients, as well as HF-related physical limitations, social limitations, self-efficacy, and health-related quality of

life. First developed in 1996 (Greene et al 2018, Spertus et al 2005), over the following two decades, the experience with the KCCQ has grown in industry-sponsored and academic studies, and it is now the most common disease PRO instrument collected in HF studies.

The study will evaluate general safety and tolerability with special focus in the incidence of AEoSIs related to skin reactions (including maculopapular rash) and infection, vital signs, clinical laboratory parameters, and ECG.

4.3 Justification for Dose

To date, 4 Phase 1 clinical studies have been completed in which a total of 36 HVs have been exposed to AZD4831 at doses 5 to 405 mg as single doses and 53 HVs at doses 2.5 to 45 mg as multiple doses. In the HV, AZD4831 was generally well tolerated with the exception of generalised maculopapular rash seen around 7-10 days after the first dose: in the single ascending dose study (D6580C00001), 1 HV out of 6 receiving 45 mg, 1 HV out of 6 receiving 135 mg and 2 HVs out of 6 receiving 405 mg; in the MAD study (D6580C00004), 2 HVs out of 8 receiving 15 mg and 2 HVs out of 5 receiving 45 mg.

In a single-blind MAD study in Japanese and Chinese HVs (Study D6580C00008), maculopapular rash was reported in 5 of 24 Japanese and Chinese HVs who received AZD4831. Maculopapular rash CTCAE Grade 1 was reported in one of 6 Japanese HVs on 5 mg AZD4831 and maculopapular rash Grade 2 was reported in one of 6 Chinese participants on 5 mg AZD4831 and in 3 of 6 Japanese HVs on 10 mg AZD4831.

A Phase 2a study intended to assess target engagement, safety, and tolerability of AZD4831 in participants with HFpEF was prematurely terminated during the COVID-19 pandemic after meeting pre-defined target engagement, safety, and tolerability criteria (Study D6580C00003). One participant out of 27 receiving 5 mg AZD4831 was discontinued from study treatment due to Grade 3 generalised maculopapular rash.

The dose selection for Part A is based on target engagement (MPO inhibition) data from the Phase 1 MAD study (HV), the Phase 2a study (HFpEF), and data from the MAD study in Japanese and Chinese healthy participants. Two dose levels are being proposed (2.5 and 5 mg) based on expected efficacy (lower dose) and safety (upper dose). The 2.5 mg dose is predicted to be the lowest clinically relevant dose (predicted to result in approximately 50% MPO inhibition) and 5 mg is the upper safety dose since no rash was observed at doses below 15 mg AZD4831 in the Phase 1 MAD study (HV), in 1 of 27 participants at 5 mg AZD4831 in the Phase 2a study (HFpEF), and in 2 of 12 HVs on 5 mg AZD4831 in the Japanese and Chinese MAD study. The dose selection for Part B will be based on totality of data in Part A, ie, safety and effect on symptoms and functions as well as effects on other biomarkers/efficacy endpoints, in order to select the dose with the predicted optimal risk/benefit ratio. The dose selection for Part B will be done by a firewalled URC (to maintain blinding) at an interim

analysis conducted when it is assessed there is a sufficient number of participants randomised and data accrued.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last protocol specified visit/assessment (including telephone contact) regardless of the number of doses of study medication they have received.

The end of the study is defined as the date of the last protocol specified visit/assessment (including telephone contact) of the last participant in the study. This would be the last participant in Part B, or Part A (the last Week 52 visit [including telephone contact] for Part A) in the event that Part B is never started.

In Part B, the EoS visit will take place 4 weeks after the final dose, which may occur upon completion of either 24, 36 or 48 weeks of treatment (see study design in Section 4). Participants who are discontinued from the IP will be encouraged to attend all the scheduled visits, including the EoS visit, which will occur 4 weeks after the initially planned final dose.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria – Part A

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 40 to ≤ 85 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Documented stable symptomatic HF (New York Heart Association Class II-IV) for at least 1 month at Screening (Visit 1) (transient HF in the setting of an MI does not qualify), with a medical history of typical signs and symptoms of HF and receiving optimal therapy for HF as determined by the health-care physician. Symptoms and signs are defined in Appendix G.

3 LVEF > 40% at Screening (Visit 1). All participants will undergo a local echocardiogram at the Screening (Visit 1) with central reading to confirm the LVEF > 40% eligibility criteria before randomisation.

4 6MWD ≥ 30 meters and ≤ 400 meters at Screening (Visit 1) and Randomisation (Visit 3). Difference in 6MWD between Screening and Randomisation must be < 50 meters.

5 KCCQ-TSS ≤ 90 points at Screening (Visit 1) and Randomisation (Visit 3).

6 NT-proBNP ≥ 250 pg/mL (sinus rhythm) or ≥ 500 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI ≤ 30 kg/m^2.
NT-proBNP ≥ 200 pg/mL (sinus rhythm) or ≥ 400 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI > 30 kg/m^2.
The ECG performed at Screening should be used for heart rhythm evaluation.

7 At least one of the following:

(a) Structural heart disease, ie, LA enlargement and/or left ventricular hypertrophy at the echocardiogram performed at Screening (Visit 1). Left atrial enlargement is defined by at least 1 of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm, or LA area ≥ 20 cm^2 or LA volume ≥ 55 mL or LAVI > 34 mL/m^2. Left ventricular hypertrophy is defined by septal thickness or posterior wall thickness ≥ 1.1 cm or LVMI > 95 g/m^2 in women and > 115 g/m^2 in men.

(b) Spectral tissue Doppler echocardiography - E/e' ratio (average of septal and lateral) ≥ 13 at rest at the echocardiogram performed at Screening (Visit 1).

(c) Indirectly estimated elevation of PASP by TRmax velocity > 2.8 m/s (280 cm/s) (PASP > 35 mmHg) at the echocardiogram performed at Screening (Visit 1) OR directly measured pulmonary capillary wedge pressure > 15 mmHg at rest within the past 12 months or > 25 mmHg at exercise documented by right heart catheterisation within 12 months prior to Screening (Visit 1).

(d) HF decompensation within 6 months before Randomisation (Visit 3), defined as hospitalisation for HF or IV diuretic treatment for HF during an urgent, unscheduled visit without hospitalisation.

Weight

8 Body mass index ≥ 18.0 kg/m^2 and ≤ 45.0 kg/m^2 (without rounding the values).

Sex

9 Male or female of non-childbearing potential.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants:

Male participants must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides, except in countries where spermicides are not approved) during treatment and until the end of relevant systemic exposure, plus a further 90-day period. Study participants must not donate or bank sperm during this same time period.

For a female partner (non-pregnant and of childbearing potential) of a male study participant, contraception recommendations should also be considered. Acceptable methods of contraception include birth control pills, injections, implants, or patches, intrauterine devices, and tubal ligation/occlusion. A barrier method is not necessary if the female partner is sterilised

Female participants:

Female participants must not be lactating and must be of nonchild-bearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy [but not tubal ligation]), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
- Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

Informed Consent

10 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

11 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative.

12 Provision of signed and dated written informed consent prior to collection of samples for optional future use blood and urine samples.

5.1.2 Inclusion Criteria – Part B

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 40 to ≤ 85 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Documented diagnosis of symptomatic HF (NYHA class II-IV) at Screening (Visit 1), and a medical history of typical symptoms/signs of heart failure ≥6 weeks before Screening (Visit 1), and receiving optimal therapy for HF as determined by the health-care physician, with at least intermittent need for diuretic treatment. Symptoms and signs are defined in Appendix G.

3 LVEF >40% and evidence of structural heart disease (ie, left ventricular hypertrophy or left atrial enlargement [1]) documented by the most recent echocardiogram, or cardiac magnetic resonance imaging within the last 12 months prior to Screening (Visit 1). If no echocardiogram is available, it can be performed at Screening (Visit 1).

[1] Structural heart disease, ie, LA enlargement and/or left ventricular hypertrophy at the echocardiogram performed at Screening (Visit 1). Left atrial enlargement is defined by at least 1 of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm, or LA area ≥ 20 cm2 or LA volume ≥ 55 mL or LAVI > 34 mL/m2. Left ventricular hypertrophy is defined by septal thickness or posterior wall thickness ≥ 1.1 cm or LVMI > 95 g/m2 in women and > 115 g/m2 in men.

4 6MWD ≥ 30 meters and ≤ 400 meters at Screening (Visit 1) and Randomisation (Visit 2). Difference in 6MWD between Screening and Randomisation must be < 50 meters.

5 KCCQ-TSS ≤ 90 points at Screening (Visit 1) and Randomisation (Visit 2).

6 NT-proBNP ≥ 250 pg/mL (sinus rhythm) or ≥ 500 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI ≤ 30 kg/m^2. NT-proBNP ≥ 200 pg/mL (sinus rhythm) or ≥ 400 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI > 30 kg/m^2. The ECG performed at Screening should be used for heart rhythm evaluation.

Weight

7 Body mass index ≥ 18.0 kg/m^2 and ≤ 45.0 kg/m^2 (without rounding the values).

Sex

8 Male or female of non-childbearing potential.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants:

Male participants must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides, except in countries where spermicides are not approved) during treatment and until the end of relevant systemic exposure, plus a further 90-day period. Study participants must not donate or bank sperm during this same time period.

For a female partner (non-pregnant and of childbearing potential) of a male study participant, contraception recommendations should also be considered. Acceptable methods of contraception include birth control pills, injections, implants, or patches, intrauterine devices, and tubal ligation/occlusion. A barrier method is not necessary if the female partner is sterilised.

Female participants:

Female participants must not be lactating and must be of nonchild-bearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy [but not tubal ligation]), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.

Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

Informed Consent

9 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

10 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative.

11 Provision of signed and dated written informed consent prior to collection of samples for optional future use blood and urine samples.

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria – Part A

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 eGFR < 30 mL/min/1.73m^2 by Chronic Kidney Disease-Epidemiology Collaboration formula at Screening (Visit 1).

2 Systolic blood pressure < 90 mmHg or ≥ 160 mmHg if not on treatment with ≥ 3 BP lowering medications or ≥ 180 mmHg irrespective of treatments at Randomisation (Visit 3)

3 Heart rate > 110 bpm or < 50 bpm at Randomisation (Visit 3).

4 Life expectancy < 3 years due to other reasons than cardiovascular disease.

5 History or ongoing allergy/hypersensitivity reactions to drugs (including but not limited to rash, angioedema, acute urticaria).

6 Presence of any disease or condition rather than HF constituting the main reason for limiting the ability to exercise/reduced exercise capacity.

7 Current decompensated HF and/or NT-proBNP > 5000 pg/mL at Screening (Visit 1)

8 Documented history of ejection fraction ≤ 40%, i.e. HF with recovered ejection fraction. Transient ejection fraction decrease e.g. in the setting of an MI does not apply.

9 Any planned cardiovascular procedure (eg, coronary revascularisation, ablation of atrial fibrillation/flutter, valve repair/replacement, aortic aneurysm surgery, etc).

10 Any cardiac event (eg, myocardial infarction, unstable angina), coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial fibrillation/flutter, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to Screening (Visit 1) or between Screening and Randomisation (Visit 3). Patients who underwent a successful atrial fibrillation/flutter cardioversion, can be enrolled in the study after 4 weeks.

11 Medical history of aborted sudden cardiac death unless protected by an implantable cardioverter-defibrillator or sustained ventricular tachycardia with haemodynamic compromise in the past 6 months.

12 Any primary cardiomyopathy (eg, genetic hypertrophic cardiomyopathy, obstructive hypertrophic, arrhythmogenic right ventricular cardiomyopathy/dysplasia), cardiomyopathies related to current toxic or infective conditions (eg, ongoing chemotherapy, myocarditis, septic cardiomyopathy), cardiomyopathies due to infiltrative diseases (eg, amyloidosis, sarcoidosis), peripartum cardiomyopathy, as well as HF due to pericardial disease, congenital heart disease or clinically significant uncorrected primary cardiac valvular disease.

13 Any past or planned organ transplantation (including cardiac), with the exception of skin transplantation.

14 Hb < 110 g/L (male) and < 100 g/L (female) or iron-deficiency with/without anaemia requiring ongoing or planned IV iron treatment.

15 Participants with hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH ≥10 mIU/mL), or any clinically significant thyroid disease as judged by the investigator.

16 Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin).

17 Acute or chronic primary liver disease with severe impairment of liver function (eg, ascites, oesophageal varices, coagulopathy). Any known and ongoing hepatitis B or C.

18 ALT or AST ≥ 2 × ULN at Screening (Visit 1).

19 Pulmonary arterial hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (ie, requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory support within 12 months prior to Screening (Visit 1).

20 Any active infection requiring oral, intravenous, or intramuscular treatment at Screening (Visit 1) and/or at Randomisation (Visit 3).

21 Prior history of drug or alcohol abuse likely to impact participant safety or compliance with study procedures as judged by the investigator or ongoing drug or alcohol abuse.

22 History of any clinically significant disease or disorder other than HF that, in the opinion of the investigator, may either put the patient at risk of participation in the study or influence the results or the patient's ability to participate in the study.

23 Any signs or confirmation of COVID-19 infection:

- Suspected (as judged by PI) or confirmed COVID-19 within the last 2 weeks prior to Screening (Visit 1) or at Randomisation (Visit 3).
- Hospitalisation for COVID-19 within the last 12 weeks prior to Screening (Visit 1).

Prior/Concomitant Therapy

24 Any concomitant medications known to be a potent CYP3A4 inducers or inhibitors, eg, itraconazole, rifampicin, clarithromycin, or propylthiouracil (refer to Section 6.5 for a list of prohibited and/or restricted medications and treatments).

Prior/Concurrent Clinical Study Experience

25 Participation in another clinical study with an Investigational Product administered in the last month prior to Screening (Visit 1) (or 5 half-lives), whichever is longer.

26 Participants with a known hypersensitivity to AZD4831 or any of the excipients of the product.

Other Exclusions

27 Involvement in the planning and/or conduct of the study (applies to both AZ staff and/or staff at the study site)

28 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements, especially completing ePRO assessments; therefore participants who are unable to read (eg, are blind or are illiterate) should be excluded from participating in this trial.

29 Previous enrolment and randomisation in the present study. (Participants who where screened and screen failed and not randomised in Part A can be screened for possible entry to Part B).

5.2.2 Exclusion Criteria - Part B

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 eGFR < 30 mL/min/1.73m^2 by Chronic Kidney Disease-Epidemiology Collaboration formula at Screening (Visit 1).

2 Systolic blood pressure < 90 mmHg or ≥ 160 mmHg if not on treatment with ≥ 3 BP lowering medications or ≥ 180 mmHg irrespective of treatments at Randomisation (Visit 2).

3 Heart rate > 110 bpm or < 50 bpm at Randomisation (Visit 2).

4 Life expectancy < 2 years due to other reasons than cardiovascular disease.

5 History or ongoing allergy/hypersensitivity reactions to drugs (including but not limited to rash, angioedema, acute urticaria).

6 Presence of any disease or condition rather than HF constituting the main reason for limiting the ability to exercise/reduced exercise capacity.

7 Current decompensated HF and/or NT-proBNP > 5000 pg/mL at Screening (Visit 1).

8 Documented history of ejection fraction ≤ 40% (ie, HF with recovered ejection fraction). Transient ejection fraction decrease (eg, in the setting of an MI does not apply).

9 Any planned cardiovascular procedure (eg, coronary revascularisation, ablation of atrial fibrillation/flutter, valve repair/replacement, aortic aneurysm surgery etc).

10 Any cardiac event (eg, myocardial infarction, unstable angina), coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial fibrillation/flutter, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to Screening (Visit 1) or between Screening (Visit 1) and Randomisation (Visit 2). Patients who underwent a successful atrial fibrillation/flutter cardioversion, can be enrolled in the study after 4 weeks.

11 HF due to any of the following: known infiltrative cardiomyopathy (eg, amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), or uncorrected primary valvular disease.

12 Any past or planned organ transplantation (including cardiac), with the exception of skin transplantation.

13 Hb < 110 g/L (male) and < 100 g/L (female) or iron-deficiency with/without anaemia requiring ongoing or planned IV iron treatment.

14 Participants with hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH ≥10 mIU/mL), or any clinically significant thyroid disease as judged by the investigator.

15 Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin).

16 Acute or chronic primary liver disease with severe impairment of liver function (eg, ascites, oesophageal varices, coagulopathy). Any known and ongoing hepatitis B or C.

17 ALT or AST ≥ 2 × ULN at Screening (Visit 1).

18 Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (ie, requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory support within 12 months prior to Screening [Visit 1]).

19 Any active infection requiring oral, intravenous, or intramuscular treatment at Screening (Visit 1) and/or at Randomisation (Visit 2).

20 Prior history of drug or alcohol abuse likely to impact participant safety or compliance with study procedures as judged by the investigator or ongoing drug or alcohol abuse.

21 History of any clinically significant disease or disorder other than HF that, in the opinion of the investigator, may either put the patient at risk of participation in the study or influence the results or the patient's ability to participate in the study.

22 Any of the following related to COVID-19:

- Suspected (as judged by PI) or confirmed COVID-19 within the last 2 weeks prior to Screening (Visit 1) or at Randomisation (Visit 2).
- Hospitalisation for COVID-19 within the last 12 weeks prior to Screening (Visit 1).

Prior/Concomitant Therapy

23 Any concomitant medications known to be a potent CYP3A4 inducers or inhibitors, eg, itraconazole, rifampicin, clarithromycin, or propylthiouracil (refer to Section 6.5 for a list of prohibited and/or restricted medications and treatments).

Prior/Concurrent Clinical Study Experience

24 Participation in another clinical study with an IP or device during the last month prior to enrolment.

25 Participants with a known hypersensitivity to AZD4831 or any of the excipients of the product.

Other Exclusions

26 Involvement in the planning and/or conduct of the study (applies to both AZ staff and/or staff at the study site).

27 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements, especially completing ePRO assessments; therefore participants who are unable to read (eg, are blind or are illiterate) should be excluded from participating in this trial.

28 Previous enrolment and randomisation in the present study. (Participants who where screened and screen failed and not randomised in Part A can be screened for possible entry to Part B).

5.3 Lifestyle Considerations

No restrictions on lifestyle are required.

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of grapefruit juice from the start of study intervention until the final dose. Study intervention can be taken with or without food.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who narrowly miss (by not more than 10%) the inclusion/exclusion criteria for eGFR and NT-proBNP may be re-tested once within 14 days.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time within the same study part if, in the opinion of the investigator, there is a reason to believe they may be eligible/fulfil the inclusion/exclusion criteria then. Participants that previously withdrew from the study are not allowed for rescreening. Rescreened participants should be assigned the same participant number as for the initial screening, and all enrolment assessments and procedures, including signing of the informed consent form, should be performed again.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 6 Investigational Products

Intervention name	Part A		Part B	
	AZD4831	Placebo	AZD4831	Placebo
Type	Drug	Drug	Drug	Drug
Dose formulation	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)	2.5 mg; 5 mg	Not applicable	2.5 mg or 5 mg	Not applicable
Dosage level(s)	2.5 mg; 5 mg; once daily [a]	Once daily [a]	2.5 mg or 5 mg; once daily	Once daily
Route of administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo-comparator	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca

Table 6 Investigational Products

Intervention name	Part A		Part B	
	AZD4831	Placebo	AZD4831	Placebo
Packaging and labelling	Study drug will be provided in bottles. Labels of bottle with AZD4831 2.5 mg will have white background and black description. Labels of bottle with AZD4831 5 mg will have green background and black description. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Study drug will be provided in bottles. Labels of bottle with AZD4831 PTM 2.5 mg will have white background and black description. Labels of bottle with AZD4831 PTM 5 mg will have green background and black description. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Study drug will be provided in bottles. Labels of bottle with AZD4831 (dose to be decided based on Part A data) will have orange background and black description. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Study drug will be provided in bottles. Labels of bottle with AZD4831 PTM (dose to be decided based on Part A data) will have orange background and black description. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.

[a] To ensure blinding to study intervention, each participant will take one tablet once daily of each type (AZD4831 2.5 mg or AZD4831 PTM 2.5 mg and AZD4831 5 mg or AZD4831 PTM 5 mg).

GMP, Good Manufacturing Practice; IMP, investigational medicinal product; NIMP, Non-investigational medicinal product; PTM, Placebo to Match.

For Part A, to ensure blinding to study intervention, participants will take study intervention from two bottles (one tablet from one bottle with white label and one tablet from one bottle with green label) once daily. Each bottle contains 35 tablets, and the participant will receive enough bottles to last until the next visit.

For Part B, participants will take study intervention from one bottle (one tablet from one bottle with orange label) once daily, for 24, 36 or 48 weeks.

The tablets are sensitive to moisture and should remain in original packaging (with desiccant) until administration. The tablets must not be chewed, crushed or divided but should be swallowed whole with water.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 For Part A: Study medication will be dispensed to participants in bottles. Participants will be instructed to take one tablet per day from two bottles (one tablet from one bottle with white label and one tablet from one bottle with green label). Each bottle contains 35 tablets and the participant will receive enough bottles to last until the next visit.

5 For Part B: Study medication will be dispensed to participants in a bottle with the dose selected on data from Part A. Participants will be instructed to take one tablet per day from the bottle. Each bottle contains 35 tablets, and the participant will receive enough bottles to last until the next visit.

6 Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM. This computerised randomisation procedure will ascertain allocation concealment and will assign the participants 1:1:1 to two dose levels of AZD4831 or matching placebo in Part A and 1:1 to AZD4831 or matching placebo in Part B. For Part A, in the event that randomisation to the AZD4831 5 mg treatment arm is stopped during the study due to safety in either the whole study or in specific countries or ethnic populations, the remaining participants in that cohort will be randomised at a 2:1 ratio to 2.5 mg AZD4831 or matching placebo.

The randomised study population will be capped by neutrophil count, 6MWD and KCCQ-TSS in both Part A and Part B. The capping will consist of:

- The proportion of participants having neutrophil count > 4×10^6/mL at Screening will be 60%-80%
- A maximum of 25% of the participants can have 6MWD ≥ 350 and ≤ 400 meters at randomisation visit.
- A maximum of 30% of the participants can have KCCQ-TSS > 80 and ≤ 90 at randomisation visit.

LVEF value at screening and atrial fibrillation/flutter status on ECG at Screening (Visit 1) may also be capped in the IRT/RTSM to avoid over- or under-representation of these participant subgroups.

The randomisation will be stratified by neutrophil count in both Part A and Part B.

The study will be blinded to both participants and Investigators/site staff as well as to the sponsor (designated sponsor personnel will be unblinded as part of DRC and URC in Part A as described in Appendix A 5). The IRT/RTSM will provide to the Investigator(s) the kit identification number to be allocated to the participant at the dispensation visit. Study intervention will be dispensed at the study visits summarised in the SoA (See Section 1.3). Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AZ, without revealing the treatment given to participant to the AZ staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented. Data in Part A will be analysed and reviewed by a URC as described in Section 9.5.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AZ, without revealing the treatment given to the participant to the AZ staff.

Pharmacokinetic samples will be analysed by the bioanalytical laboratory performing the bioanalyses only for participants on active treatment, as referenced in Section 8.5.1.1. To allow for the appropriate selection of samples, the bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study.

6.4 Study Intervention Compliance

The first dose of study intervention will be administered in clinic on the day of randomisation. Participants will receive study intervention at the site on visit days and at home between visits.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision, after checking treatment was not taken at home before coming to the study site. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Participants will be provided with a dosing card to record the date and time of last dose taken the day before the clinic visit for the purposes of PK evaluation.

A record of the number of AZD4831/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

COVID-19 vaccines received during the study and prior to study entry are to be recorded; the type of vaccine is also to be recorded.

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

The following medications and treatments are prohibited and/or restricted:

- Strong inhibitors of CYP3A4, including grapefruit juice

- Strong inducers of CYP3A4 such as nevirapine, rifampicin, carbamazepine, fosphenytoin, pentobarbital, phenobarbital, phenytoin, primidone, rifapentine, enzalutamide, lumacaftor, St. John's Wort, mitotane, apalutamide, quinine, rimexolone, rifaximin, rifamycin, topiramate, qsymia, oxcarbazepine, midostaurin
- Cyclosporin or Tacrolimus
- Protease inhibitors such as ritonavir, indinavir, nelfinavir, saquinavir, atazanavir, darunavir, lopinavir, tipranavir
- Macrolide antibiotics: clarithromycin, telithromycin
- Chloramphenicol (antibiotic)
- Azole antifungals, ie, ketoconazole, itraconazole, posaconazole, voriconazole
- Nefazodone (antidepressant)
- Cobicistat
- Propylthiouracil
- Silymarin

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Intervention After the End of the Study

There is no planned intervention following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant should remain in the study, ie, continue to participate in scheduled study visits and evaluations.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. For procedures in the case of withdrawal from the study, see Section 7.2.

At each visit, participants will be instructed to contact the investigator immediately, if rash or skin reaction has developed. If maculopapular rash grade 1, 2, or 3 has developed, participant must be permanently discontinued from the study intervention and AZ medical staff should be informed.

- Grade 1: Macules/papules covering < 10% Body Surface Area with or without symptoms (eg, pruritus, burning, tightness).

- Grade 2: Macules/papules covering 10 - 30% Body Surface Area, with or without symptoms (eg, pruritus, burning, tightness); limiting Instrumental ADL (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc); rash covering > 30% Body Surface Area with or without mild symptoms.
- Grade 3: Macules/papules covering > 30% Body Surface Area, with moderate or severe symptoms; limiting Self-care ADL (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

If the participant develops a rash or skin reaction that is not considered a maculopapular rash, but is a generalised rash/skin reaction or is considered to be an SAE, the participant must be permanently discontinued from the study intervention and AZ medical staff should be informed.

For further information and skin reaction evaluation guidance, see Appendix B 5.

Study participants also may be discontinued from study intervention in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event or other safety reasons as judged by the Investigator and/or sponsor where continued treatment may put the participant at undue risk.
- Development of uncontrolled and clinical significant CCI as judged by the Investigator.
- Severe non-compliance with the CSP.
- Pregnancy

At the time of permanent discontinuation of study intervention, an Early Discontinuation visit should be conducted. See the SoA (See Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Every attempt should be made to maintain participants on the study intervention during the course of the study. If the study intervention has been interrupted, it should be re-introduced as soon as, in the opinion of the Investigator, the participant is able to re-start study treatment. Note related to AEoSI skin reactions (including maculopapular rash): In the occurrence of maculopapular rash CTCAE Grade 1, 2, or 3, or any other generalised rash/skin reaction or serious rash/skin reaction, study intervention should be permanently discontinued. At each visit, participants will be instructed to stop the study intervention and contact the investigator immediately if rash or skin reaction has developed. After the participant has been seen by the study doctor or designee and the skin reaction is not considered a maculopapular rash CTCAE

Grade 1, 2, or 3, or any other generalised rash/skin reaction or serious rash/skin reaction, the study treatment can be restarted.

7.1.2 Rechallenge

Participants who have temporarily discontinued study intervention can resume treatment as soon as, in the opinion of the Investigator, the participant is able to re-start study treatment and the participant wishes to resume. No minimum time period is necessary before treatment can resume.

If a participant develops maculopapular rash CTCAE Grades 1, 2, or 3 or any other generalised rash/skin reaction or serious rash/skin reaction, study intervention should be permanently discontinued.

7.2 Participant Withdrawal from the Study

A participant may withdraw from the study (eg, withdraw consent) at any time (study intervention and assessments) at his/her own request, without prejudice to further treatment, or may be withdrawn at any time at the discretion of the investigator for behavioural, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an EDV should be conducted, as shown in the SoA (See Section 1.3). If the participant is discontinued from study intervention, and later decides to withdraw from the study before scheduled EoS visit, the EoS visit should be performed at the time of withdrawal. See the SoA (See Section 1.3) for data to be collected at the EDV and EoS visit. For procedures in the case of discontinuation from study intervention, see Section 7.1.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site and vital status not found in publicly available sources at the end of the study.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 318 mL (Part A) and approximately 300 mL (Part B). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Patient Reported Outcomes

Participants will perform the PRO assessments using an electronic tablet during clinic visits CCI) at the timepoints indicated in the SoA (See Section 1.3). CCI . All questionnaires, except the PRD-acute version for the 6MWT, must be completed using the electronic tablet (or the web-based backup, in case of technical failure or if the participant forgets to bring the device to the clinic). The PRD-acute version will be recorded by site staff in the eCRF. Each site must allocate the responsibility for the administration of the PROs to a specific site personnel and, if possible, assign a back-up person to cover if that individual is absent. A key aspect of study success is to have high PRO compliance. Therefore, it is essential that site personnel follow the SoA (See Section 1.3) and ensure that the device is charged and set up properly before the participant comes for the visit.

If participants have any medical problems, they should discuss them with their doctor or research nurse separately from the PRO assessment.

The research nurse or appointed site staff must remind participants there are no right or wrong answers and that the value and relevance of PRO data is to hear directly from participants, without interpretation from health care professionals or others, how they function and feel.

Site staff must administer questionnaires available in the language that the participant speaks and understands. Questions should not be read in an available language and translated into another language for the participant.

The following best practice guidelines should be followed:

- The PRO questionnaires must be completed after signed consent but before any other study procedures are conducted, including being seen by the doctor, with the exception of the PRD-acute version which is to be completed before the 6MWT.
- The appointed site personnel must show participants how to use the electronic PRO device, in accordance with the instructions provided.

- To avoid bias participants must not receive help from relatives, friends or site staff to answer or to clarify the PRO questionnaires.
- The PRO questionnaires must be completed by the participant in privacy.
- The participant should be given enough time to complete the PRO questionnaires at his or her own speed.

On completion of the questionnaires during clinic visits, the tablet should be handed back to the designated responsible person, who should check that all questionnaires, relevant for the specific visit (See Section 1.3), were completed. If any PRO questionnaire was not completed the site personnel must document the reason why a participant could not complete assessments in the eCRF.

- The appointed site personnel should also stress that the information is confidential. Therefore, if the participant has any medical problems, he or she should discuss them with the doctor or study nurse separately from the PRO assessment.

The following PROs will be used in this study:

Part A

- KCCQ
- CCI [redacted]
- [redacted]
- [redacted]

Part B

- KCCQ
- PGIS-HF
- PGIS-WD
- PRD-acute version
- CCI [redacted]

Baseline PROs will be collected at the Randomisation visit (Visit 3 and Visit 2 for Part A and Part B, respectively).

CCI [redacted]

8.1.1.1 Kansas City Cardiomyopathy Questionnaire

The KCCQ is a psychometrically validated questionnaire developed for patients with congestive HF (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 summarised and transformed to a score of 0 to 100; higher scores indicate better health status. Total symptom score will be calculated to assess the frequency and burden of clinical symptoms. The KCCQ English US Master version is enclosed in Appendix H.

8.1.1.2 Patient Global Impression of Severity in Heart Failure Symptoms

The PGIS-HF (Appendix I) item assesses how a participant perceives his or her overall severity of HF symptoms over the past two weeks. Participants will choose from 6 response options ranging from ‘no symptoms’ to ‘very severe’.

8.1.1.3 Patient Global Impression of Severity in Walking Difficulties

The PGIS-WD (Appendix J) item assesses how a participant perceives his or her current overall limitation in walking ability. Participants will choose from 6 response options ranging from ‘no limitations’ to ‘very severe limitations’.

8.1.1.4 Patient Rating of Dyspnoea, Acute Version

The PRD-acute version (Appendix K) is a single question item asking the participant to rate his or her shortness of breath right now on a scale from 0 to 10, where 0 indicates ´No shortness of breath´ and 10 ‘As bad as you can imagine’.

This item will be collected as part of the 6MWT and recorded by site staff in the eCRF.

8.1.1.5 CCI

[redacted]

8.1.2 CCI

[redacted]

8.1.3 6 Minute Walk Test

The 6MWT will be conducted based on the ATS guidelines at the timepoints specified in the SoA (See Section 1.3). The clinical research staff will receive appropriate training on how to perform the test. As far as possible, for each participant, the test should be performed in the

same location, by the same study personnel, and at the same time of day (in the morning, if possible) in order to minimise within- participant variability.

CCI [redacted]

After completing the PRD-acute version, the participant will walk as far as he or she can in 6 minutes. The 6MWD will be assessed under standard test conditions, in accordance with the ATS guidelines.

CCI [redacted]

When the oxygen saturation is measured immediately before and after the test, it is important to keep the finger at heart level (IC4) for standardised measurement.

If the participant uses oxygen therapy for a HF condition, its use during the test should be recorded (including the volume/min) and be kept consistent during each 6MWT. If the participant is wearing a face mask, eg, due to COVID-19, it should also be recorded and should be used consistently thereafter for each test.

8.1.4 Echocardiogram

8.1.4.1 Echocardiogarm – Part A

Transthoracic echocardiographic images will be obtained at the timepoints specified in the SoA (See Section 1.3). Transthoracic echocardiography examination will be performed with participants at rest in the best position for optimal image acquisition. Standard adult clinical cardiac transducers will be used for 2D, M-mode, colour Doppler, and tissue Doppler imaging, as detailed in the echocardiography imaging manual that will be supplied to all study sites. Doppler and tissue Doppler echocardiography will be performed to obtain indices necessary for comprehensive assessment of LV systolic and diastolic function and non-invasive haemodynamic measurements. Finally, 2D images of the LV will be obtained and optimised (with frame rate 50-80 frames per second) for off-line 2D speckle tracking analysis. Imaging personnel and equipment will be undergo certification by a separate, blinded to study treatment, independent core laboratory.

Baseline echocardiogram will be performed at screening for all participants to confirm eligibility. Images will be sent to the core laboratory for analysis and interpretation. If for any

reason an echocardiogram image is deemed uninterpretable for any planned measurements by the core laboratory, then echocardiography may be repeated at the discretion of the investigator, participant, and Medical Monitor. The repeat echocardiogram should be obtained within 7 days of the previous test whenever possible apart from the screening echocardiogram, where should a repeat be needed, this can be obtained more than 7 days after the first screening echocardiogram, however, this must be performed so that the results are available to assess study eligibility prior to randomisation (Visit 3). If Visit 8 or Visit 9 echocardiogram cannot be repeated within 7 days, the repeat echocardiogram can be performed if it occurs within 28 days of initial echocardiogram and no later than study Day 141 (Visit 8) or Day 211 (Visit 9).

Planned measurements include but are not limited to:

- LV-GLS: left ventricular global longitudinal strain
- LAVI: left atrial volume index
- LVEF: left ventricular ejection fraction
- LVMI: left ventricle mass index
- CCI [redacted]

The complete list of parameters is described in the echocardiogram imaging manual/charter.

The de-identified echocardiographic images may be transferred to the sponsor at the end of the study or before for potential future scientific health-related research.

8.1.4.2 Echocardiogram – Part B

Echocardiogram will be performed at Screening (Visit 1) unless there is an available echocardiogram or cardiac magnetic resonance imaging performed up to 12 months before Screening (Visit 1). Echocardiogram will be performed according to local procedures, without central reading.

8.1.5 Assessment of CV Events

To evaluate the effect of AZD4831 vs placebo on CV events, the following will be collected in Part A and Part B: HF hospitalisation, urgent HF visits with requirement for additional loop diuretic treatment, MI, CV deaths, and all-cause mortality. Unstable angina, urgent coronary revascularization, and cerebrovascular events are not considered endpoints of this study, but will also be collected in the specific eCRF. See Appendix M for definitions of HF hospitalization and urgent HF visit.

8.1.6 Study Participant Feedback Questionnaire (Part A only)

This study will include an option for participants to complete an anonymised questionnaire, ‘Study Participant Feedback Questionnaire’ (Appendix N) for participants to provide feedback

on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect, or AEs and, therefore, would not be study data. The questionnaire is completed at the timepoints specified in the SoA (See Section 1.3).

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (See Section 1.3)

8.2.1 Physical Examinations

A full physical examination, performed at Visits 1, 8, and 11/EDV in Part A and at Visits 1 and EoS visit/EDV in Part B, will include assessments of the following; general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen (liver and spleen) including waist circumference, musculoskeletal (including spine and extremities) and neurological systems. On other occasions as specified in the SoA, either a skin examination only, or a brief physical examination will be conducted and will include, at a minimum, assessments of the following: general appearance, skin, abdomen (liver and spleen), and musculoskeletal, cardiovascular, and respiratory systems.

Physical examination as well as assessments of height and weight will be performed at timepoints as specified in the SoA (See Section 1.3). Body mass index will be calculated at Visit 1: BMI = weight/(height)^2, where weight is measured in kg, and height in metres.

8.2.2 Vital Signs

Vital signs (supine BP [average of 3 measurements], pulse rate, and body temperature) will be performed at timepoints as specified in the SoA (See Section 1.3).

The measurements should be done before any blood sampling or the exercise testing. The measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.2.2.1 Vital Signs - Part A only

At Visit 3 and Visit 6 for Part A, the vital signs BP measurements can be used for the pre-dose supine measurements for the orthostatic test, if taken after being supine for at least 10 minutes and as long as the standing BP measurements are taken after these supine measurements at the time intervals described below for the orthostatic blood pressure measurement.

<u>Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension (Part A only)</u>

For participants in Part A, orthostatic BP measurements will be obtained at baseline (Visit 3) and at Week 12 (Visit 6) during the treatment period using a standard sphygmomanometer and

taken after scheduled supine measurements (1 and 3 minutes after the participant stands) and prior to any required blood draw or study intervention (to be measured pre dose at Day 1 [Visit 3] and pre dose at Week 12 [Visit 6]).

To minimise chances of orthostatic hypotension related to volume depletion, participants should be well hydrated when they come to the clinic for study visits. Supine BP measures will be collected after participants have been lying down for at least 10 minutes. To ensure that a stable supine BP is obtained, at least 2 systolic and 2 diastolic BP measurements will be obtained. If the replicate measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine BP will be considered stable. The mean value of each replicate (mean systolic and mean diastolic value) will represent the baseline BP for that visit. After stable BP is achieved, the participant will stand and a BP measurement will be taken at 1 and 3 minutes after the participant stands. If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed. If the BP measurement meets the criteria shown in Table 7, investigators will repeat the supine and standing measurements up to 2 additional times.The exception is for participants with orthostatic hypotension symptoms: in this situation, the orthostatic hypotension AE should be reported based on a single orthostatic test sequence.

When evaluating orthostatic vitals, record any symptoms of dizziness or light headedness. Record on the AE page in the eCRF.

Table 7 Orthostatic Blood Pressure Criteria and Management

Decrease in BP indicative of orthostatic hypotension	Actions
≥ 20 mmHg systolic or ≥ 10 mmHg diastolic	Repeat the BP measurements (supine and standing) up to 2 additional times, unless orthostatic hypotension is present in association with symptoms related to the measurement of orthostatic vitals: in such a case the test doesn't need to be repeated and the orthostatic hypotension AE and symptoms related to the measurement of orthostatic vitals AE should be reported based on a single sequence. • If either the 1 minute or 3 minute standing BP meets the orthostatic (postural) hypotension criteria, then the sequence is considered indicative of orthostatic hypotension. • If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is confirmed and an AE of orthostatic hypotension will be reported.

For participants with orthostatic hypotension, individualised treatment should be prescribed at the investigator’s discretion following local guidelines, including pharmacological (eg, down titration of nitrates) or non-pharmacological (eg, hydration) treatments.

8.2.3 Electrocardiograms

Single 12-lead ECG (standard ECG with a paper speed of 25-50 mm/second covering at least 6 sequential beats) will be obtained after the participant has been resting in a supine position for at least 5 minutes, at the visits outlined in the SoA (See Section 1.3). A digital ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals will be used. Interpretation of the clinical safety digital ECG findings will be reviewed and confirmed by the Investigator and recorded in the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA (See Section 1.3).

Additional safety samples, including ANCA samples, may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and type of sample will be recorded on the appropriate eCRF.

The clinical chemistry and, haematology, will be performed at a central laboratory. Dipstick urinalysis will be performed locally.

The following laboratory variables will be measured:

Table 8 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	
B-Hb	B-Leukocyte differential count (absolute count and percent differential)
B-Leukocyte count	B-Platelet count
haematocrit	MCV
MCHC	MCH
RDW	reticulocyte
Clinical Chemistry (serum or plasma)	
S-Creatinine	S-Albumin
S-Bilirubin, total	S-Potassium
S-Bilirubin, direct	
S-Bilirubin, unconjugated, ie, indirect (total – direct)	S-Calcium, total
S-ALP	S-Sodium
S-AST	S-Creatine kinase
S-ALT	Glucose
Free T4 and total T4	Chloride
T3	Bicarbonate

Table 8 Laboratory Safety Variables

TSH	Phosphorus
Magnesium	S-Uric Acid [a]
Urinalysis (dipstick)	
U-Hb/Erythrocytes/Blood	U-Glucose
U-Protein/Albumin	
Immunology	
c-ANCA[b]	p-ANCA
Other assessments	
FSH (females only, at screening)	

[a] Serum samples sent to the central laboratory for serum uric acid safety assessment will also be used as part of the exploratory biomarker assessment at Visit 3, Visit 8, and Visit 11/EDV (Part A).

[b] The ANCA sample collected at baseline is only to be tested upon requirement ie, appearance of maculopapular rash, based on investigator discretion. An additional sample should be collected if clinically indicated.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, whole blood; c-ANCA, cytoplasmic staining anti-neutrophil cytoplasmic antibodies; FSH, follicle-stimulating hormone; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; p-ANCA, perinuclear-anti-neutrophil cytoplasmic antibodies; RDW, red cell distribution width; S, serum; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; U, urine.

Note: In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

Blood samples for the determination of c-ANCA and p-ANCA will be assayed by bioanalytical test sites operated by or on behalf of AZ, using appropriately validated bioanalytical methods.

Analysis of c-ANCA and p-ANCA will be performed by an indirect immunofluorescent assay. For samples that test positive, titres of the specific ANCA will subsequently be evaluated. In addition, positive samples will also be tested using MPO and proteinase 3 fluorescent microparticle immunoassays. These analyses will be performed at a central laboratory.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.2.5 Skin Reactions, Including Maculopapular Rash

Skin reactions, including maculopapular rash, will be considered AEs of special interest in this study. To ensure that data are collected systematically, any skin reaction will be recorded on a special eCRF page. All skin reactions should be recorded in the eCRF as an AE or SAE. If the rash is considered maculopapular, it will be evaluated using CTCAE grades 1-3 for rash maculopapular; if not considered maculopapular, severity will be captured as

mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), body surface area impacted, anatomical site(s), symptoms, signs, effect on participant (including ADL impacted), concomitant medications, medication administered, and specific rash diagnosis, if available. Photos (overview and detailed) should be taken.

Please refer to Appendix B 5 for further guidance in rash assessment and reporting.

At all visits, participants will be instructed to contact the investigator immediately if rash or skin reaction has developed at any time point during the study. Participants will be recommended to make an acceptable quality self-photo of skin affected with rash/skin reaction.

If any study participant develops a confirmed generalised maculopapular rash CTCAE grade 1-3, throat tightness or angioedema at any time during the study, the investigator should immediately stop the study drug and arrange for the participant to receive the appropriate medical treatment relevant to this situation.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical exam and collection of blood samples for safety, hsCRP, and PK. If a participant is discontinued from investigational product and proceeds to the EDV, an exploratory biomarker sample and blood and urine samples for exploratory metabolite analysis will also be collected. The mandatory genetic sample per Section 8.6.3 should also be collected at the EDV if not previously collected from the participant. It is suggested to start the treatment with a topical steroid and/or oral antihistamine. The treatment should be individualised per participant and based on PI discretion. Upon PI discretion, a clinical dermatologist can be consulted and a skin biopsy considered. The participant can be provided with a treatment for the skin rash, according to clinical management standard. Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

8.2.6 Infection

Infections will be considered AE of special interest in this study. Local laboratory testing for microorganisms per local guidelines is requested for serious infections (those that meet SAE criteria) and results documented.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of the first dose throughout the treatment period and including the follow-up period (final follow up is Visit 12 for Part A and Visit 8 for Part B). The only exception is related to the pre-dose orthostatic test at Visit 3: if orthostatic hypotension is confirmed, it should be reported as an AE, and symptoms related to the measurement of orthostatic vitals if present should also be reported as an AE.

SAEs will be recorded from the time of signing of the informed consent form.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant’s last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Maximum CTCAE grade for rash maculopapular
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused participant’s withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- In case of fatality:
  - Probable cause of death
  - Date of death
  - Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated measurements should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AZ representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative will work with the investigator to ensure that all the necessary information is provided to the AZ Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AZ representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AZ representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AZ representative by telephone. The AZ representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

The reference document for definition of expectedness/listedness is the IB for the AZ drug.

8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AZ except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.8.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AZ.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study and is discovered after the first dose, then the investigator or other site personnel informs the appropriate AZ representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.7) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.8.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study until 3 months after the final Follow-up Visit.

In case of pregnancy in the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participants's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should, if possible, be obtained and documented.

8.3.9 Medication Error

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AZ representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.7) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.3.9.1 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.9.2 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of investigational product greater than those specified in this protocol within the same day will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AZ study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AZ representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.7) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled or individual pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of AZD4831 as specified in the SoA (See Section 1.3). Pharmacokinetic Samples will be collected pre-dose; thus, participants should be reminded not to take their study medication at home on the day of their clinic visit as they will receive study medication in clinic on these days. Therefore, the last dose of study medication at Visit 11 for Part A, and either Visit 5, Visit 6 or Visit 7 for

Part B will be in clinic. For Part A, in a subset of participants where sites are able, additional post-dose PK samples will be collected at Visit 6 at the timepoints specified in the SoA. For participants who are discontinued from investigational product due to rash, a PK sample should be collected at the discontinuation visit. Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Plasma samples will be used to analyse the PK of AZD4831. Samples collected for analyses of AZD4831 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AZ, using an appropriately validated bioanalytical method. Full details of the analytical method used 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.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

Placebo samples will not be analysed unless there is a need to confirm that correct treatment has been given to study participants.

8.5.2 Pharmacodynamics

8.5.2.1 Collection of Samples

Blood samples will be collected for measurement of NT-proBNP, hsCRP, and IL-6 as specified in the SoA (See Section 1.3).

An additional 5 mL blood sample may be collected for a NT-proBNP quick test to be performed on-site for pre-screening purposes; this test will be analysed locally and will not be sent to the central laboratory. The test must be recorded by site staff on the Pre-screening Log with a date and note of potential eligibility per Inclusion Criterion 6 (See Section 5.1) as Y/N based on the test result. The pre-screening test does not replace the NT-proBNP sampling at the Screening (Visit 1) (See Section 1.3), which will be sent to the central laboratory.

Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual.

For storage, re-use, and destruction of pharmacodynamic samples, see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Blood Samples for [redacted]

Blood samples for exploratory quantification of [redacted] are required and will be collected from participants in Part A and B of this study as specified in the SoA (See Section 1.3).

Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use and destruction of samples see Section 8.5 and Appendix C.

8.6.2 Collection of Mandatory Samples for Exploratory Biomarker and Metabolite Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Blood samples for exploratory biomarker research are required and will be collected from all participants in this study as specified in the SoA (See Section 1.3). Plasma and serum samples will be collected for the analysis of biomarkers that may respond to treatment of AZD4831 and/or that may predict response to treatment with AZD4831, including but not limited to:

[redacted]

For Part A, exploratory analysis of [redacted] will be performed at the timepoints specified in the SoA (See Section 1.3). Exploratory analysis of AZD4831 metabolites in plasma will also be performed at the timepoints specified in the SoA (See Section 1.3).

Where CCI is part of the parameters measured from blood samples collected for safety assessment and analysed at the central laboratory, the parameter from the sample collected for the safety assessment will be used for the exploratory biomarker analysis.

CCI will be analysed through local laboratory and entered in the appropriate eCRF page.

For Part A, for participants who discontinue investigational product due to rash or skin reaction, blood and urine will be collected at the EDV for exploratory biomarker analysis in blood and analysis of AZD4831 metabolites in urine and plasma. For Part B, only blood (plasma) will be collected for analysis of AZD4831 metabolites.

Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use and destruction of exploratory samples, see Section 8.5 and Appendix C.

8.6.3 Collection of Mandatory Sample for Genetic Analysis

A blood sample will be collected for mandatory genetic analysis by AZ or designated organisation(s). This sample will be used to prepare DNA to assess the genotype of certain genes that may be related to how the investigational drug is metabolised by the participant's body and/or to the development of skin reactions. Genotyping will include, but will not be limited to, an assessment of the human leukocyte antigen genes. The genetic research may involve the genotyping of selected genes or the analysis of the whole genome sequence. The sample will only be used for these purposes as outlined.

The blood sample for genetic research will be obtained from the participants at Visit 3 and Visit 2 for Part A and Part B, respectively.

If for any reason the sample is not drawn at these visits, it may be taken at any visit until the last study visit. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.6.4 Collection of Mandatory Samples for Potential Diagnostic Assay Development

Plasma and serum samples for potential diagnostic development are required and will be collected from all participants in Part A and B of this study as specified in the SoA (See Section 1.3). The intention of these samples is to provide additional samples for assessment of the variability in levels of candidate biomarkers that show potential to predict response to treatment with AZD4831 and to bridge from a Research Use Only assay to a diagnostic assay. The samples may be used for commercial diagnostic assay development.

Plasma and serum samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use and destruction of samples, see Section 8.5 and Appendix C.

8.6.5 Collection of Optional Samples for Future Biomarker Research

Collection of plasma, serum and urine samples for future biomarker research is also part of this study for both Part A and B as specified in the SoA (See Section 1.3) and is subject to agreement to optional consent.

Plasma, serum and urine samples will be collected for the future exploratory analysis of biomarkers that may respond to treatment with AZD4831 or that predict response to treatment with AZD4831. Distinct from the mandatory collection of exploratory samples, these samples may be used to analyse exploratory biomarkers not defined in the CSP and may include multiplex analysis using biomarker panels.

Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use and destruction of exploratory samples, see Section 8.5 and Appendix C.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (See Section 1.3) and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Part A – 6MWD and KCCQ-TSS change from baseline at 16 weeks:

The primary statistical test has the null hypothesis that there will be no difference between AZD4831 and placebo regarding mean change from baseline for the primary efficacy variables at 16 weeks.

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

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

Part B – 6MWD change from baseline at 24 weeks:

The primary statistical test has the null hypothesis that there will be no difference between AZD4831 and placebo regarding mean change from baseline for the primary efficacy variables at 24 weeks.

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

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

Part B - KCCQ-TSS change from baseline at 24 weeks:

The null hypothesis will be that neither the treatment group nor treatment-by-baseline interaction terms explain the expected change from baseline in KCCQ-TSS, ie:

H0: β_3=β_4 = 0, versus the alternative hypothesis:

H1: $\beta_3 \neq 0$ or $\beta_4 \neq 0$ or both.

Where β_3 is the coefficient for treatment group and β_4 is the coefficient for the treatment-by-baseline interaction term. See Section 9.4.2.1 for model specification details.

9.2 Sample Size Determination

	Part A	**Part B**
Enrolled	Estimated 1100 participants	Estimated 1350 participants
Randomised	Estimated 660 participants	Estimated 820 participants
Participants with complete safety data	Estimated 600 participants	Estimated 745 participants

Part A

The sample size selection was based on the following assumptions:

- Change from baseline in 6MWD is approximately normally distributed with a standard deviation of 70 meters (Nassif et al 2019).
- Change from baseline in KCCQ-TSS is approximately normally distributed with a standard deviation of 18 points.

Approximately 660 participants randomised, of which we estimate approximately 600 will have complete safety data, and 1:1:1 allocation, is chosen to have enough participants exposed to AZD4831 at the therapeutic dose to fulfil the minimum requirement in the ICH E1 guideline on population exposure, taken together with Part B of this study, as well as a second function and symptom study with a similar design as Part B, and Phase 1 studies completed ahead of submission.

With 85% power at a significance level of $\alpha = 0.05$, 200 participants per arm will allow detection of a difference of 6.0 points in mean change from baseline between active and placebo in KCCQ-TSS comparing each active arm with placebo. The critical value for statistical significance is 3.9 points. The corresponding numbers for 6MWD are 21 meters and 14 meters. Calculations of detectable differences and critical values are based on ANCOVA, which will also be used for the analysis.

The potential effect of informative censoring, including all-cause mortality, will be considered during the analysis of the data and interpretation of the results, but not taken into account in the sample size calculations for Part A.

Part B

For part B, we assume that the type 1 error is controlled using Bonferroni adjustment (this is not necessarily the choice of method for type 1 error control in the analysis phase).

For KCCQ-TSS, we assume that:

- Change from baseline in KCCQ-TSS is approximately normally distributed with an expected value dependent on the baseline score, treatment group and treatment-by-baseline interaction, and with a residual error of 18.
- For KCCQ-TSS, due to the assumed treatment-by-baseline interaction, the power was assessed through simulation of normally distributed values truncated to the range [0, 100]. Simulated studies are analysed with ANCOVA with an interaction effect between treatment group and baseline KCCQ-TSS. The global null hypothesis of no impact of treatment group on the expected change from baseline is assessed by a likelihood-ratio test comparing this model to a model with no treatment effects.

Approximately 820 participants will be randomised in 1:1 allocation, of which we estimate approximately 745 will have complete safety data. The sample size is chosen to have enough participants exposed to AZD4831 at the therapeutic dose to fulfil the minimum requirement in the ICH E1 guideline on population exposure, taken together with Part A of this study as well as a second function and symptom study with a similar design as Part B, and Phase 1 studies completed ahead of submission.

With the proposed number of participants, and under the alternative hypothesis for the treatment effect represented by the line $y = 18.2 - 0.112*BASE_{KCCQ\text{-}TSS}$ for the difference in expected change from baseline with AZD4831 compared to placebo as a function of the baseline score, the global null hypothesis can be rejected in more than 99% of simulations.

For 6MWD, change from baseline in 6MWD is assumed to be approximately normally distributed with a standard deviation of 70 meters. Power calculations are based on a two-sample t-test with shared variance. Assuming a true difference in mean change from baseline of 19 meters, the power to reject the null hypothesis is 95% with the proposed number of participants. The critical value is 11.

9.3 Populations for Analyses

Part A

Full Analysis Set:

All participants who have been randomised to study treatment and who have received at least one dose of investigational product will be included in the Full Analysis Set irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised study medication assignment, irrespective of the treatment actually received.

Safety Analysis Set:

The Safety Analysis Set consists of all participants who have received at least one dose of investigational product. Erroneously treated participants (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A participant who has received any dose of the experimental IP will be classified as in the experimental IP treatment group.

Part B

Full Analysis Set:

All participants who have been randomised to study treatment and who have received at least one dose of investigational product will be included in the Full Analysis Set irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised study medication assignment, irrespective of the treatment actually received.

Efficacy and safety analyses in Part B will be done on the Full Analysis Set.

9.4 Statistical Analyses

The Statistical analysis plans will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violations have been identified and documented. The only exception are study independent personnel who are involved in the interim analyses in Part A. Analyses will be performed by AZ or its representatives.

Nominal significance levels will be 0.05 and all tests performed will be two-sided. All confidence intervals will be 95%.

For Part A, baseline will be defined as the last non-missing value on or before the day of first dose and on or before the day of randomisation (whatever occurs first), individually for each participant and endpoint. The baseline value for safety analyses is the last non-missing value prior to administration of the first dose of IP.

In Part B, for subjects who receive first administration of IP on the day of randomisation, the baseline value for statistical analysis of safety parameters is the last non-missing value prior to the administration of the first dose of IP. For subjects where the first administration of IP takes place after the day of randomisation, the baseline is defined as relative to the day and timepoint of randomisation instead of actual day of first administration of IP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary efficacy endpoints are KCCQ-TSS and 6MWD and the primary efficacy variables are change from baseline in KCCQ-TSS and 6MWD at 16 weeks for Part A and at 24 weeks for Part B.

All primary variables will be analysed using ANCOVA with baseline and treatment group as covariate, and will be adjusted for the stratification factor for neutrophil count (Part A and Part B), comparing the AZD4831 doses versus placebo. For Part A, both single doses alone, and both doses pooled, will be compared with placebo. In Part B, a term for treatment by-baseline interaction will be included as independent variable in the model for KCCQ-TSS.

Model summary in Part A:

- 6MWD change from baseline at 16 Weeks:

$$E[CHG_{6MWD}|BASE_{6MWD}, TRT] = \beta_0 + \beta_1 * BASE_{6MWD} + \beta_2 * STRATA + \beta_3 * TRT$$

- KCCQ-TSS change from baseline at 16 Weeks:

$$E\left[CHG_{KCCQ-TSS}\,\middle|\,BASE_{KCCQ-TSS}, TRT\right] = \beta_0 + \beta_1 * BASE_{KCCQ-TSS} + \beta_2 * STRATA + \beta_3 * TRT$$

Model summary in Part B

- 6MWD change from baseline at 24 Weeks:

$$E[CHG_{6MWD}|BASE_{6MWD}, TRT] = \beta_0 + \beta_1 * BASE_{6MWD} + \beta_2 * STRATA + \beta_3 * TRT$$

- KCCQ-TSS change from baseline at 24 Weeks:

$$E\left[CHG_{KCCQ-TSS}\middle|BASE_{KCCQ-TSS}, TRT\right] = \beta_0 + \beta_1 * BASE_{KCCQ-TSS} + \beta_2 * STRATA + \beta_3 * TRT + \beta_4 * BASE_{KCCQ-TSS} * TRT$$

Where TRT indicates randomized treatment group; STRATA indicates neutrophil baseline strata; $BASE_{6MWD}$ and CHG_{6MWD} indicates baseline and change from baseline in 6MWD, respectively; and $BASE_{KCCQ\text{-}TSS}$ and $CHG_{KCCQ\text{-}TSS}$ indicates baseline and change from baseline in KCCQ-TSS, respectively.

Subgroup analyses will be performed for both primary endpoints.

Primary Efficacy Objectives Related Estimands:

Part A:

Treatment: Treatment with 2.5 mg or 5 mg AZD4831 compared to placebo, administered in addition to optimal back-ground therapy for co-morbidities.

Population: Patients that fulfill all of the inclusion criteria, none of the exclusion criteria and have available measurements of the efficacy endpoint at baseline and 16 weeks.

Endpoint: Change from baseline to 16 weeks in KCCQ-TSS and 6MWD.

Intercurrent events: Patients with intercurrent events resulting in missing assessments of the primary endpoints, eg, terminal events or withdrawal from the study, is expected to be very few and will be excluded from the analysis (principal stratum strategy). Other intercurrent

events, eg, premature discontinuation of study treatment, will be ignored (treatment policy strategy).

Population-level summary: Difference in adjusted mean change from baseline between groups.

Missing data will not be imputed.

Part B:
Treatment: Treatment with either 2.5 mg or 5 mg AZD4831 compared to placebo, administered in addition to optimal back-ground therapy for co-morbidities.

Population: Patients that fulfill all of the inclusion and none of the exclusion criteria.

Endpoint: Change from baseline to 24 weeks in KCCQ-TSS and 6MWD.

Intercurrent events:

- Deaths will be handled by a While-alive strategy, implemented by using the change from baseline to 24 weeks or last measurement prior to death (if earlier than 24 weeks).
- Intercurrent events other than deaths will be handled by a Treatment-policy strategy, ie, measurements will be collected and used in the statistical analysis regardless of the occurrence of the event

Population-level summary: Between group difference in mean change from baseline at 24 weeks or prior to death, if earlier. For KCCQ-TSS, this will be a function of baseline values.

For patients with missing measurements for reasons other than death, a multiple imputation scheme will be employed, which differentiates between monotonous and non-monotonous missing data. Monotonous missing data are where observations are consistently missing after a point in time whereas non-monotonous missing data are missing observations followed by at least one recorded observation. For monotonous missing data, retrieved dropouts (patients remaining in the study despite same intercurrent events as drop-outs) will be used to impute missing values or, if there are too few retrieved dropouts, a Jump-to-reference approach utilizing placebo patients will be applied.

As a supplementary approach, analyses where deaths are combined with the outcome variables in a Composite strategy will be conducted, and will be described in the SAP for Part B.

Methods for multiplicity control, both Part A and Part B:
The endpoints will be tested using an overall 2-sided alpha level of 0.05. Multiplicity across primary and secondary endpoints will be accounted for by utilising a pre-specified testing

procedure of the primary and secondary endpoints (and potentially among doses in Part A) and alpha recycling will be considered using a weighted group sequential recycling procedure following the approach of Burman et al (2009), (Ye et al 2013). Details will be described in the SAPs.

9.4.2.2 Secondary Endpoint(s)

The secondary efficacy endpoints for Part A are 6MWD and KCCQ-TSS (at 24 and 48 weeks), NT-proBNP, IL-6, and hsCRP (at 16, 24, and 48 weeks), LV-GLS, LAVI, and LVMI (at 16 and 24 weeks), and pharmacokinetic concentrations. The secondary efficacy endpoints for Part B are NT-proBNP, IL-6, and hsCRP (at 24 weeks). The secondary efficacy variables will be change from baseline in 6MWD, LV-GLS, LAVI, and LVMI for Part A and NT-proBNP, IL-6, and hsCRP for Parts A and B, and will be analysed in the same manner as for the primary endpointof 6MWD. The secondary efficacy variable of KCCQ-TSS will be analysed in the same manner as for the primary endpoint of KCCQ-TSS. NT-proBNP, IL-6, and hsCRP will be analysed by applying log scale.

Plasma concentrations of AZD4831 will be summarised by timepoints and dose level. If PK data permit, PK parameters, eg, AUC and C_{max}, will be derived but also a population PK model will be developed, possibly with the support of PK data from other studies, using nonlinear mixed effects regression analysis in NONMEM. Furthermore, if data allows, the population PK model may be coupled with separate PD models. All PK/PD modelling will be described in a separate data analysis plan. Moreover, the derived PK parameters and the results of any such modelling will be provided in a separate PK and population PK/PD report (as an appendix to the CSR or as a stand-alone report).

9.4.2.3 Tertiary/Exploratory Endpoint(s)

Tertiary/exploratory endpoints will be described in the SAPs.

9.4.3 Safety

Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory variables, and ECG . In addition, extra evaluation will be done for the following Adverse Events of Special Interest (AEoSI): skin reactions, including maculopapular rash, and infections (see Section 8.2). Exposure to study treatment will be described.

Safety analyses will be performed using the safety analysis set in Part A, and using the full analysis set in Part B. Safety data will be presented using descriptive statistics unless otherwise specified.

Safety analyses will be performed for two different study periods: on-study and on-treatment. These periods are defined in the Part A SAP and Part B SAP, respectively.

Safety Estimand Definition

The aim with the analyses of safety data is to assess the general safety objective, evaluated in a scenario where study treatment is not prematurely discontinued. Two analysis approaches are considered complementary to assess this hypothetical scenario for all safety endpoints:

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

Hence, the general safety objective will be assessed through an estimand defined by the following attributes:

Population: Patients that fulfill all of the inclusion and none of the exclusion criteria..

Treatment: Treatment with either 2.5 mg or 5 mg of AZD4831 compared to placebo, administered in addition to optimal back-ground therapy for co-morbidities.

Intercurrent events:

- Premature study treatment discontinuation: All analyses will be provided using two complementary approaches.
    - Hypothetical as premature study treatment discontinuation cannot occur, implemented by excluding/censoring data after premature study treatment discontinuation + 14 days.
    - Treatment policy by ignoring study treatment discontinuation, implemented by including all available data.
- Initiation or change of concomitant medication, including rescue medication: Will be ignored, that is, handled using a treatment policy approach.
- Death: With the exception of assessment of mortality, will be handled hypothetically as it cannot occur, implemented by censoring time to event data at death and not imputing any data after death.

Population level summaries: Distribution of endpoints by treatment group, Kaplan-Meier estimate for endpoints by treatment group, difference in Kaplan-Meier estimates between treatment groups and treatment hazard ratios.

This estimand requires that to the extent possible, randomised subjects are followed up regardless of study intervention compliance and adherence to the study protocol.

Adverse Events

All AEs will be classified by system organ class, high level group term, high level term, and preferred term according to MedDRA.

AEs will be presented for each treatment group by SOC and/or PT, covering number and percentage of subjects reporting at least one event. An overview of AEs will present for each treatment group the number and percentage of subjects with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. Separate AE tables will be provided taking into consideration seriousness, death, and events leading to discontinuation of IP. An additional table will present number and percentage of subjects with most common AEs. Most common (eg, frequency of >x%, ≥x%) will be defined in the SAP. In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of subjects in any treatment group. Key subject information will be presented for subjects with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. An AE listing for the safety analysis set will cover details for each individual AE. AEoSIs related to skin reactions, including maculopapular rash, and infection will be presented. Full details of AE analyses will be provided in the SAP.

All safety analyses are descriptive; hence no p-values will be presented for any safety analyses, and confidence intervals are provided as an illustration of precision of the estimate. Hazard ratio between treatment groups will be based on a Cox proportional hazards regression model with a factor for treatment group.

Treatment emergent

For Part A, the definition for treatment emergent events will be provided in the SAP.

For Part B, the following AEs are considered treatment emergent: AEs with an onset date on or after baseline or a worsening of pre-existing AEs on or after baseline. A treatment emergent abnormality is defined as a switch in a safety parameter from not-abnormal at baseline to abnormal at post-baseline assessments accordingly to predefined criteria specified in the SAP.

Vital signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline. Details of vital sign analyses will be provided in the SAP.

In Part B, time to first treatment emergent abnormality will also be presented.

Laboratory

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline. A frequency table presents number of subjects reporting at least one treatment emergent change in selected laboratory parameters. Details of laboratory analyses will be provided in the SAP.

In Part B, time to first treatment emergent abnormality will also be presented.

Electrocardiogram

Electrocardiogram evaluation will be summarised and presented by treatment group for baseline and for each scheduled post-baseline assessment. More details of ECG analyses will be provided in the SAP.

9.4.4 Other Analyses

For any digital devices used in the study, summaries of the related variables will be made and comparisons between treatment arms will be assessed descriptively.

9.5 Interim Analyses

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

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

For details on Data Review Committee, Unblinded Review Committee, and Data Monitoring Committee, refer to Appendix A 5

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AZ.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance

Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

Data Review Committee: For part A, an unblinded DRC will be set up for ongoing, periodic safety monitoring, with a focus on skin reactions. The DRC consists of internal sponsor expertise, an external dermatologist, and an external cardiologist. More information on roles, responsibilities, and procedures will be contained in the DRC charter.

Unblinded Review Committee: A URC consisting of a limited number of sponsor personnel will be formed to review data from Part A for at least one, but possibly several, interim analyses, with the purpose of informing further development of the clinical programme, including but not limited to dose selection for Part B. The URC will review the risk/benefit

profile and make recommendations on the dose for Part B and, based on safety, on the continuation of the program. When all participants in Part A have completed Week 52, the URC will review data for the last interim analysis to help inform further clinical development.

External Data Monitoring Committee: For Part B, an independent DMC, including a dermatologist, will be appointed and will report to the sponsor. The DMC will be responsible for safeguarding the interests of the participants by assessing the safety of the study treatment during the study and making appropriate recommendations based on the available data. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing. A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the sponsor.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that

the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in source data verification plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. Part B will start following analysis of Part A. The sponsor will inform sites when Part B can be started.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or Good Clinical Practice guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AZ study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole

- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose

- Someone who is not enrolled in the study intentionally takes the drug

B 5 Guide to skin reaction assessment

This Appendix describes the process to be followed to appropriately identify, assess and report cases of skin reactions. Skin reactions, including maculopapular rash, will be considered AEs of special interest in this study. To ensure that data are collected systematically, any skin reaction will be recorded on a special eCRF page. All skin reactions should be recorded and reported as AEs or SAEs.

If the rash is considered maculopapular, it will be evaluated using CTCAE grades 1-3 for rash maculopapular; if not considered maculopapular, severity will be captured as mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), body surface area impacted, anatomical site(s), symptoms, signs, effect on participant (including ADL impacted), concomitant medications, medication administered, and specific rash diagnosis, if available.

If maculopapular rash Grade 1, 2, or 3 has developed, participant must be permanently discontinued from IP, and AZ medical staff should be informed.

If the participant develops a rash or skin reaction that is not considered a maculopapular rash, the participant must permanently discontinue if the rash/skin reaction is considered an SAE or is a generalised rash/skin reaction. AstraZeneca medical staff should be informed.

At all visits, participants will be instructed to contact the investigator immediately if rash has developed at any time point during the study. Participants will be recommended to make an acceptable quality self-photo of skin affected with rash.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical examination and blood samples for safety, hsCRP, and PK. If a participant is discontinued from investigational product and proceeds to the EDV, exploratory biomarker sample and blood and urine samples for exploratory metabolite analysis will also be collected. The mandatory genetic sample per Section 8.6.3 should also be collected at the EDV if not previously collected from the participant. Initiation of treatment with a topical steroid and/or oral antihistamine is suggested. The treatment should be individualised per participant and based on Investigator discretion. Upon Investigator discretion, a clinical dermatologist can be consulted and a skin biopsy considered. The

participant can be provided with a treatment for the skin rash, according to clinical management standard. Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

Investigator should make quality photo(s) of participant's skin affected with rash, that will allow the evaluation of rash according to the guidance given in this section.

The Common Terminology Criteria for AEs is a descriptive terminology that can be used for AE reporting.

In general, CTCAE Guideline describes the Grades of AE severity from 1 to 5:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*

Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

***Instrumental Activities of Daily Living (ADL)** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

****Self-care Activities of Daily Living (ADL)** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: for Maculo-Papular rash, only 3 CTC Grades exist:

Maculo-Papular Rash	
Definition: A disorder characterised by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.	
Grade 1	Macules/papules covering < 10% Body Surface Area with or without symptoms (eg, pruritus, burning, tightness)
Grade 2	Macules/papules covering 10 - 30% Body Surface Area, with or without symptoms (eg, pruritus, burning, tightness); limiting Instrumental Activities of Daily Living*; rash covering > 30% Body Surface Area with or without mild symptoms
Grade 3	Macules/papules covering > 30% Body Surface Area, with moderate or severe symptoms; limiting Self-care Activities of Daily Living **

Ref: (NCI 2017)

To assess the Body Surface Area (BSA) affected by rash, please follow the algorithm described below:

Area	Number of palms	Percent area
Whole body	100	100%
Head and Neck	10	10%
Upper extremities	20	20%
Trunk	30	30%
Lower extremities	40	40%

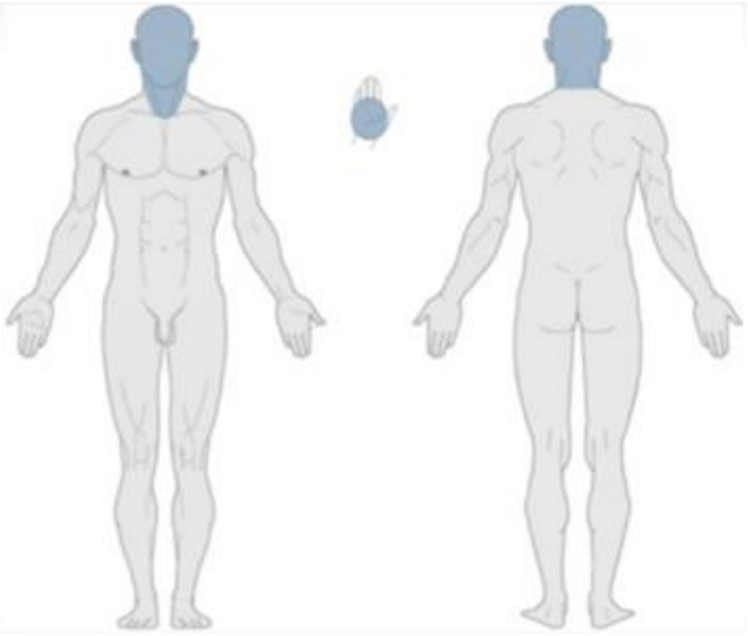
The participant's palm is defined as "1", representing 1% of total Body Surface Area (BSA).

Total BSA = 100% (100 palms).

The neck is included as part of the head

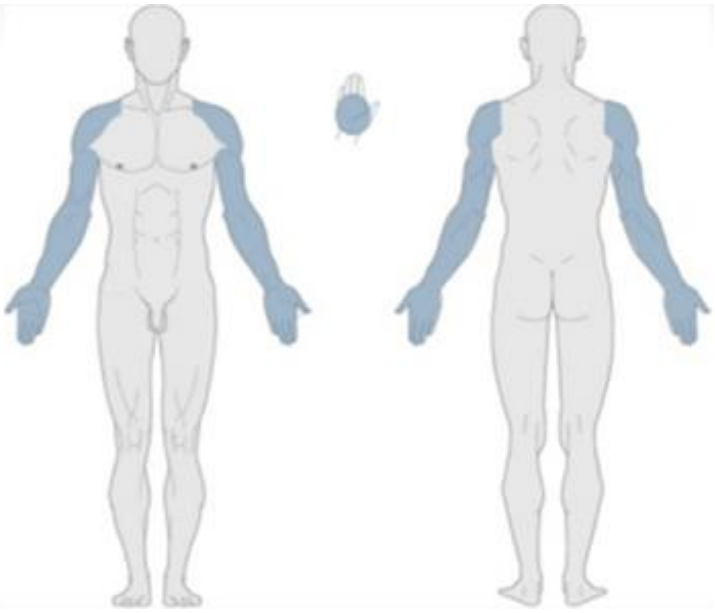
Head and Neck = 10% (10 palms)

Patient's palm = **1%**
Total BSA = **100%** (100 palms)



Upper extremities = 20% (20 palms)

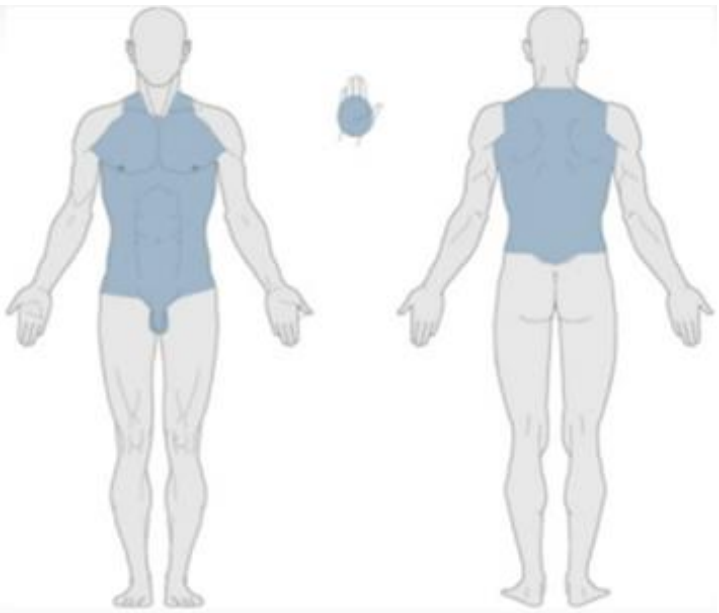
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The axillae and genitals are included with the trunk

Trunk (axillae and groin) = 30% (30 palms)

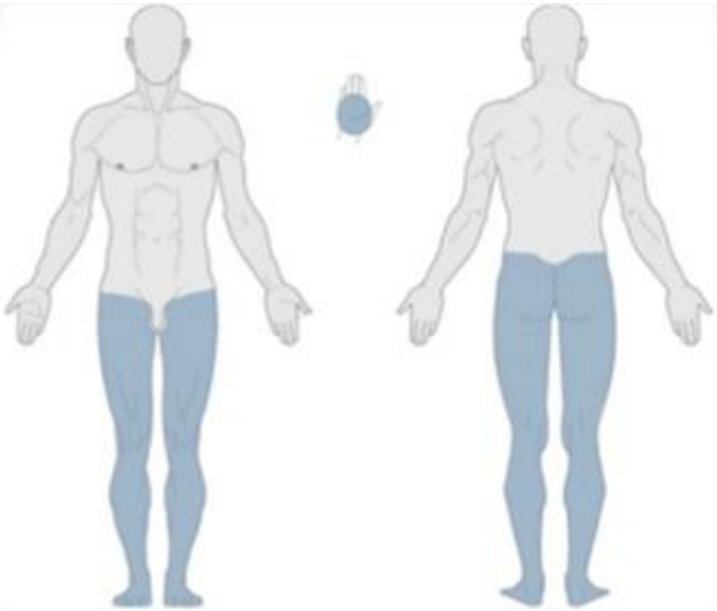
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The inguinal canal separates the trunk and legs anteriorly

Lower extremities (buttocks included) = **40%** (40 palms)

Patient's palm = **1%**
Total BSA = **100%** (100 palms)



Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AZ Team for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AZ is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AZ or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AZ are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- The 6 mL K2 EDTA blood sample for this genetic research will be obtained from the participants at Visit 3 and Visit 2 in Part A and Part B, respectively Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AZ genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AZ employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AZ or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AZ Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AZ and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AZ clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AZ representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AZ representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AZ representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AZ representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's law lab kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AZ Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a]HBV DNA is only recommended when IgG anti-HBc is positive
[b]HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c]CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 7 References

FDA Guidance for Industry, July 2009

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation


CCI

Appendix G Typical Symptoms and Signs of Heart Failure

Symptoms

- Breathlessness
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Reduced exercise tolerance
- Fatigue, tiredness
- Increased time to recover after exercise.

Signs

More specific:

- Elevated jugular venous pressure (JVP)
- Hepatojugular reflex
- Third heart sound (gallop rhythm)
- Laterally displaced apical impulse.

Less specific:

- Weight gain (>2 kg/week)
- Weight loss (in advanced HF)
- Tissue wasting (cachexia)
- Cardiac murmur
- Peripheral oedema (ankle, sacral, scrotal)
- Pulmonary crepitations
- Reduced air entry and dullness to percussion at lung bases (pleural effusion)
- Tachycardia, irregular pulse
- Tachypnoea, Cheyne Stokes respiration
- Hepatomegaly
- Ascites
- Cold extremities
- Oliguria
- Narrow pulse pressure.

Appendix H Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

 Original US English

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

 Original US English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

 Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

 Original US English

Appendix I Patient Global Impression of Severity in Heart Failure Symptoms

Patient Global Impression of Severity for Heart Failure Symptoms

Overall, how would you rate the severity of your heart failure symptoms over the past 2 weeks?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

Appendix J Patient Global Impression of Severity in Walking Difficulties

Patient Global Impression of Severity in Walking Difficulties

Overall, how would you rate your walking ability today?

☐ No limitations

☐ Very mild limitations

☐ Mild limitations

☐ Moderate limitations

☐ Severe limitations

☐ Very Severe limitations

Appendix K Patient Rating of Dyspnoea (PRD) – Acute Version

Patient Rating of Dyspnoea (PRD) – acute version

How would you rate your shortness of breath right now?

0	1	2	3	4	5	6	7	8	9	10
No shortness of breath										As bad as you can imagine

Appendix L EuroQol 5-dimension 5-level Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

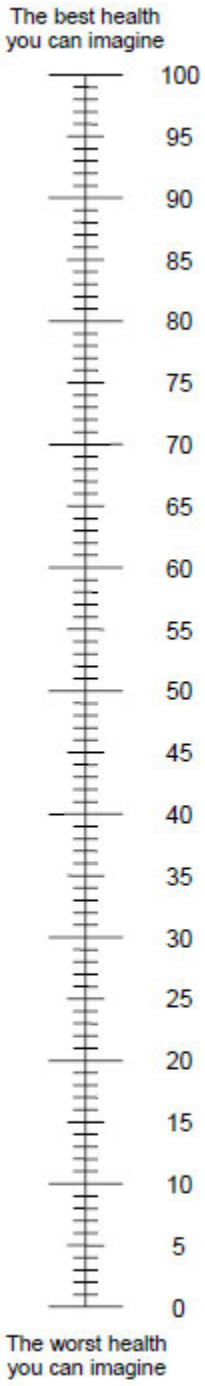
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix M Clinical Data Interchange Standards Consortium Definition for Hospitalisation for Heart Failure and Urgent Heart Failure Visit

An **HF Event** includes hospitalisation for HF and may include urgent outpatient visits. Heart Failure hospitalisations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalisations.

Heart Failure Hospitalisation is defined as an event that meets **ALL** of the following criteria:

1 The patient is admitted to the hospital with a primary diagnosis of HF

2 The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3 The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:

   (a) Dyspnoea (dyspnoea with exertion, dyspnoea at rest, orthopnea, paroxysmal nocturnal dyspnoea)

   (b) Decreased exercise tolerance

   (c) Fatigue

4 The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:

   (a) Physical examination findings considered to be due to HF, including new or worsened:

      - Peripheral oedema
      - Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
      - Pulmonary rales/crackles/crepitations
      - Increased jugular venous pressure and/or hepatojugular reflux
      - S3 gallop
      - Clinically significant or rapid weight gain thought to be related to fluid retention

   (b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

      - Increased BNP/NT-proBNP concentrations consistent with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

- Radiological evidence of pulmonary congestion.
- Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract minute stroke distance (time velocity integral).

OR

- Invasive diagnostic evidence with right heart catheterisation showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5 The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:
   (a) Augmentation in oral diuretic therapy
   (b) Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator)
   (c) Mechanical or surgical intervention, including:
      - Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
      - Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

An **Urgent HF Visit** is defined as an event that meets all of the following:

6 The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalisation.

7 All signs and symptoms for HF hospitalisation (ie, symptoms and physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met.

8 The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Appendix N Study Participant Feedback Questionnaire

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

Patient Experience Initiative

Study Participant Feedback Questionnaire (SPFQ)

Version 1.1

Prepared by:

TransCelerate Patient Experience Initiative Team

Section A: Your experience before you started the study <to be completed within 1 month of study enrollment>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select one response for each item

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
1. I Understand the treatment process in this trial (for example: when and how to take or use a treatment)					
2. The information given to me before I joined the trial was everything I wanted to know (for example: visits and procedures, time commitment, who to contact with questions).					
3. The information given to me before I joined the trial was easy for me to understand (for example: visits and procedures, time commitment, who to contact with questions).					
4. I felt comfortable that I could ask any questions before I joined the trial.					
5. I am comfortable with using the Activity monitor watch at home for this trial					
6. I am comfortable with using the Holter monitor patch (if applicable) at home for this trial					
7. I was adequately informed on how to use the Activity monitor watch in this trial.					
8. I was adequately informed on how to use the Holter monitor patch (if applicable) in this trial.					
9. I am comfortable completing the KCCQ questionnaire (electronic) at home for this trial					
10. I am comfortable with performing the 1-minute-sit-to-stand test at home for this trial					

Section B: Your experience during the trial <to be completed during trial progress>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select one response for each item

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
1. Overall, I am satisfied with the trial site (for example: comfort and privacy of treatment area, waiting area, parking, ease of access to the site)					
2. My trial visits have been well organized					
3. My trial visits are scheduled at a convenient time for me					
4. The staff treats me with respect					
5. I feel comfortable that I can ask questions during the trial					
6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					
9. I was provided with a Thank You Card for my participation in this trial					
	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
10. I am comfortable with using the Activity monitor watch at home for this trial					
11. I find the Activity monitor watch is easy to use					
12. I am comfortable with using the Holter monitor patch (if applicable) at home for this trial					

13. I find the Holter monitor patch is easy to use					
14. I am comfortable completing the KCCQ questionnaire (electronic) at home for this trial					
15. I am comfortable with performing the 1-minute-sit-to-stand test at home for this trial					

Section C: Your experience at the end of the trial <to be completed at last trial visit>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select one response for each item

	NO		YES		
1. I was informed when I had completed the trial					
2. I was informed of any future opportunities to access the overall trial results if I wanted to					
	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
3. Overall, I was satisfied with the information I received about future support after the trial (for example: future treatment, follow-up contact details)					
4. Overall, I was satisfied with my trial experience					
	Much less than expected	Somewhat less than expected	Same as expected	Somewhat more than expected	Much more than expected
5. Compared to when the trial started, the overall commitment required was similar to what I expected					
	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
6. Overall, I was comfortable with using the Activity monitor watch at home for this trial					
7. Overall, I found the Activity monitor watch easy to use					
8. Overall, I was comfortable with using the Holter monitor patch (if applicable) at home for this trial					
9. Overall, I found the Holter monitor patch (if applicable) easy to use					

10. Overall, I was comfortable completing the KCCQ questionnaire (electronic) at home for this trial					
11. Overall, I was comfortable with performing 1-minute-sit-to-stand test at home for this trial					

Appendix O COVID-19 Specifics

O 1 Introduction

The COVID-19 pandemic has had a striking impact on health care, as well as on ongoing and prospective clinical studies. Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. As the threat of pandemic burden including new outbreaks, locally or globally, may impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff, and society as a whole.

O 2 Risk Assessment for COVID-19 Pandemic

While there is a theoretical risk that treatment with an MPO inhibitor could impair host-defense mechanisms, an increased incidence of infection has not been seen in limited clinical data with AZD4831; therefore, the risk to participants exposed to SARS-CoV-2 or to those who suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular HF. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

AstraZeneca has no data on the co-administration of AZD4831 and COVID-19 vaccines being approved. Potential AZD4831 vaccine interactions affecting patient safety or IMP and vaccine efficacy are therefore unclear.

O 3 Measures to Mitigate the Risks Associated with COVID-19

National laws and local recommendations regarding the pandemic will be strictly adhered to.

The probability of virus transmission will be controlled as much as possible by considering:

- Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
- Confirmation of COVID-19 by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator’s discretion.
- Requesting all participants to be contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs, including fever, dry cough, dyspnoea, sore throat, and fatigue and are asked not to attend the site in case of suspected reports. In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.

- Physical distancing and person-to-person contact restrictions will be applied during site visits.
- Where physical distancing is not possible, personal protective equipment will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

O 4 Suspected or Confirmed COVID-19

O 4.1 Prior to Enrolment

Prior to Screening (Visit 1), participants should be called to confirm they are not experiencing any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat and fatigue. The participants with suspected ongoing (as judged by PI) or not completely resolved COVID-19 at Screening (Visit 1) will not be enrolled in the study. If the participant has a positive SARS-CoV-2 reverse transcription-polymerase chain reaction test result within 2 weeks before Screening (Visit 1), the participant will not be enrolled in the study. Furthermore, the participants who have previously been hospitalised with SARS-CoV-2 infection within the last 12 weeks, will not be enrolled in the study. Excluded participants will be treated according to standard of care.

O 4.2 At Randomisation

The participants with suspected ongoing (as judged by PI) or confirmed COVID-19 at Randomisation (Visit 3 and Visit 2 for Part A and Part B, respectively), will be excluded from the study, and treated according to standard of care.

O 4.3 After Randomisation

If the participant becomes symptomatic after screening, and has suspected (as judged by PI) or confirmed COVID-19, regardless of severity of the symptoms and potential hospitalisation, the participant may temporarily or permanently discontinue study intervention at the discretion of the site investigator.

O 5 References

Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020).
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on June 03, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix P Abbreviations

Abbreviation or special term	Explanation
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADL	Activities of Daily Living
AE	adverse event
AEoSI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ANCA	anti-neutrophil cytoplasmic antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase/transaminase
ATS	American Thoracic Society
AZ	AstraZeneca
BP	blood pressure
BMI	body mass index
BNP	brain natriuretic peptide
$_{C}$-ANCA	cytoplasmic staining anti-neutrophil cytoplasmic antibody
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DRC	Data Review Committee
E/e’	Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
ECG	electrocardiogram
Echo	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation or special term	Explanation
EQ-5D-5L	EuroQol Five-dimensional Five-level Questionnaire
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
Hb	haemoglobin
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HL	Hy's Law
HLT	High-Level Terms
hsCRP	high-sensitivity C-reactive protein
HV	healthy volunteer(s)
HV	healthy volunteer
IB	Investigator's Brochure
IATA	International Airline Transportation Associations
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-6	interleukin 6
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LAVI	left atrial volume index
LV	left ventricle
LVEF	left ventricle ejection fraction
LV-GLS	left ventricular global longitudinal strain
LVM	left ventricular mass
LVMI	left ventricular mass index
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction

Abbreviation or special term	Explanation
MPO	myeloperoxidase
MPOi	MPO inhibitor
NIMP	Non Investigational Medicinal Product
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
p-ANCA	perinuclear-anti-neutrophil cytoplasmic antibody
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamics
PGIS-HF	Patient Global Impression of Severity in Heart Failure
PGIS-WD	Patient Global Impression of Severity in Walking Difficulties
PHL	Potential Hy's Law
PI	Principal Investigator
PK	pharmacokinetic(s)
PRD	Patient Rating of Dyspnoea
PRO	patient reported outcome
PT	Preferred Terms
RNA	ribonucleic acid
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SOC	System Organ Class
TBL	total bilirubin
TSS	total symptom score
UACR	urinary albumin to creatinine ratio
ULN	upper limit of normal
URC	Unblinded Review Committee

Appendix Q Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

Amendment 3 (09 February 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

To broaden entry criteria for KCCQ-TSS, modify entry criteria for NT-ProBNP. Some clarification to text is also included. All changes and the rationale are listed below.

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 4.3 Justification for Dose, Section 6.3 Measures to Minimise Bias: Randomisation and Blinding, Section 8.1.1 Patient Reported Outcomes, Section 9.5 Interim analysis, Appendix A5 Committees Structure	Wording on interim analysis updated to add possibility for further interim analyses for Part A	To allow for further interim analyses during Part A	Substantial
Section 1.1 Synopsis, , Section 9.2 Sample Size Determination	Part A change from baseline clarified as mean change	Clarification	Non-substantial
Section 1.2 Schema	Figure 1 updated to clarify safety follow-up is double blind and to updated interim analysis timing	Clarification	Non-substantial
Section 1.3 Schedule of Activities, Table 1, Part A. Footnote G	Revised text: Once approximately 20% of participants have been tested, no further participants would ~~not~~ need this additional post dose sampling	Correction	Non-substantial
Section 1.3 Schedule of Activities, Table 1, Part A. Footnote H	Wording updated to separate the calculation of UACR from central laboratory.	UACR not calculated by central laboratory, calculation done by sponsor	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.3 Schedule of Activities, Table 1, Part A. Footnote K	Included in the footnote for Echo that for Visit 8 and Visit 9 the Echo can be done at the earliest opportunity and within 7 days of the clinic visit if it cannot be performed on the same day as the clinic visit due to Echo scheduling.	To add flexibility for participant scheduling	Non-substantial
Section 1.3 Schedule of Activities, Table 1, Part A. Footnote M, Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Added for pre-dose orthostatic test at Visit 3: if orthostatic hypotension is confirmed, it should be reported as AE, and symptoms related to the measurement of orthostatic vitals if present should also be reported as an AE	To clarify that if orthostatic hypotension is confirmed on the pre-dose orthostatic test that this still be reported as AE even though before IMP to be consistent with wording in Section 8.2.2 vital signs and for clearer identification and assessment of cases of orthostatic hypotension.	Non-substantial
Section 5.1 Inclusion Criteria (Inclusion criterion 2) and Appendix G	Heart failure criterion revised	Simplification of the criteria	Non-substantial
Section 5.1 Inclusion Criteria (Inclusion criterion 5)	KCCQ-TSS points at Screening (Visit 1) and Randomisation (Visit 3) changed from ≤ 80 to ≤ 90	Due to high screen failure rate this inclusion criterion has been broadened. However, a maximum of 30% of the participants can have KCCQ-TSS > 80 and ≤ 90 at randomisation visit. This cap has been added to Section 6.3.	Substantial
Section 5.1 Inclusion Criteria (Inclusion criterion 6)	Wording added that the ECG performed at Screening should be used for heart rhythm evaluation for this Inclusion criterion.	Clarification	Non -Substantial
Section 5.1 Inclusion Criteria (Inclusion criterion 6)	Added that adjustment for NT-proBNP is now made for BMI.	To accommodate the lower levels of NT-proBNP that can be observed in obese patients	Non-substantial
Section 5.1 Inclusion Criteria (Inclusion criterion 7c)	Added alternative TRmax velocity units.	To align with the unit that appears on the central core laboratory report.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 5.2 Exclusion Criteria (Exclusion criterion 8)	Clarified that patients should be excluded if they have HF with recovered ejection fraction. Transient ejection fraction decrease eg, in the setting of an MI does not apply.	Clarification	Non-substantial
Section 5.2 Exclusion Criteria (Exclusion criterion 20)	Added that exclusion is for active infection requiring oral, intravenous or intramuscular treatment	Clarification	Non-substantial
Section 5.2 Exclusion Criteria (Exclusion criterion 24)	Any concomitant medications known to be associated with Torsades de Pointes: wording associated with Torsades de Pointes removed.	QTc exposure/response modelling confirming no QTc prolongation after administration of AZD4831 at predicted and supra therapeutic exposure levels.	Non-substantial
Section 5.4 Screen Failures	Added that NT-proBNP can also be re-tested once if Inclusion criterion 6 is not met, providing the result is not lower than 10% below the inclusion cut off	To allow for re-test of NT-proBNP on the low end value. Re-test of NT-proBNP is already allowed on the high end value in Exclusion criteria 7	Non-substantial
	Requirement for rescreen to be after at least 30 days removed	Restriction is not needed and this adds flexibility	Non-substantial
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Added that the study will also be capped for KCCQ-TSS	With the change to the inclusion criteria for KCCQ-TSS to ≤90, a cap has been added that a maximum of 30% of the participants can have KCCQ-TSS > 80 and ≤ 90 at randomisation visit in order that participants entering on the higher range are not over represented.	Non-substantial
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Cap on neutrophil count adjusted for > 4×10^6/mL from 70% to 60%-80%	To add flexibility for recruitment without compromising the scientific intent.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 8.1.4 Echocardiography	Clarified that the independent core laboratory will be blinded to study treatment	Clarification	Non-substantial
Section 8.2.2 Vital Signs	Included “Visit 6” in the text that for Part A the repeated supine blood pressure measurement can also be used as the pre-dose supine measurement for the orthostatic test as long as the required conditions are met.	To reduce the number of repeated blood pressure measurements at Visit 6	Non-substantial
	Added that at Visit 3, if orthostatic hypotension is confirmed pre-dose and post-dose, the orthostatic hypotension AE should be reported twice (pre-dose and post-dose)	Clarification	Non-substantial
	Added guidance related to reporting of symptoms related to the measurement of orthostatic vitals	Clarification	Non-substantial
Section 9.4.2.1 Primary Endpoint(s)	Wording “stratified by” corrected to “adjusted for” neutrophil count	To allow for other methods of accounting for the randomisation stratification variable.	Non-substantial

AE, adverse event; BMI, body mass index; ECG, electrocardiogram; Echo, echocardiogram; HF, heart failure; IMP, Investigational Medicinal Product; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; QT, ECG interal measured from the beginning of the QRS complx to the end of the T wave; QTc, corrected QT interval; SAE, serious adverse event; TSS, total symptom score; UACR, urinary albumin to creatinine ratio.

Amendment 2 (01 November 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

To reduce the complexity of the study by removing some exploratory assessments and optional assessments to reduce the burden to both participants and sites. Some clarification to text is also included. All changes and the rationale are listed below.

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 1.1 (Synopsis: Objectives and Endpoints)	Observed value and absolute change from baseline values over time for ECG measurements removed and replaced with investigator evaluation.	Correction as observed values are not being collected only investigator evaluation	Non-substantial
Section 1.1 (Synopsis: Data Monitoring Committee)	Addition of a further external member	Request of French regulatory authority	Non-substantial
Section 1.2 (Schema: Figure 1 Study Design - Part A)	Removal of 1MSTST, activity monitor, Holter Patch, retinal scans, and CPET	Simplification of the CSP	Non-substantial
Section 1.2 (Schema: Figure 2 Study Design - Part B)	Removal of Visit "8" as no longer applicable due to removal of activity monitor – subsequent visit numbers (9, 10 and 11) changed to 8, 9, and 10	Simplification of the CSP	Non-substantial
Section 1.2 (Schema: Figure 2 Study Design - Part B)	Footnotes a and b included	To align with presentation in the Schema for Part A	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A)	Removal of optional informed consent collection for retinal scan	Retinal scans are no longer being performed in this study.	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, and associated footnote)	Removal of 1MSTST with oximeter	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A)	Removal of ANCA samples at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 52 Follow-up	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A)	Removal of complement samples	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, and associated footnote)	Removal of activity monitor	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, and associated footnote)	Removal of placement of Holter patch	Simplification of the CSP	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, and associated footnotes)	Removal of CPET	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, and associated footnote)	Removal of collection of digital retinal photographs	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A)	Removal of optional Paxgene blood sample for RNA analysis	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A)	Additional AE/SAE assessments introduced at Visits 2 and 7	To align assessments with the timing of telephone contact by site	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, footnote a)	Text added to indicate that telephone contact will be made by the site at Visits 2 and 7 to remind participants of the need to complete remote KCCQ	To assist participant with management of the electronic PRO assessment device at home	Non-substantial
Section 1.3 (Schedule of Activities: Table 1 – Part A, footnote h)	Text added to indicate creatinine and albumin will also be collected at Visits 3, 8, and 11 along with calculation of UACR	Sample added as a biomarker of endothelial dysfunction for prognostic evaluation in the study population	Non-substantial
Section 1.3 (Schedule of Activities: Table 2 – Part B)	Removal of Visit “8” as no longer applicable due to removal of the activity monitor – subsequent visit numbers (9, 10, and 11) changed to 8, 9, and 10 Removal of ANCA samples at Week 4, Week 12, and Week 28 Follow-up Removal of complement samples	Simplification of the CSP	Non-substantial
Section 1.3 (Schedule of Activities: Table 2 – Part B, and associated footnote)	Removal of activity monitor dispense and collection	Simplification of the CSP	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 1.3 (Schedule of Activities: Table 2 – Part B)	Additional AE/SAE assessments introduced at Visits 2, 6 and 7	To align assessments with the timing of telephone contact by site	Non-substantial
Section 1.3 (Schedule of Activities: Table 2 – Part B footnote a)	Text added to indicate that telephone contact will be made by the site at indicated visits to remind participants of the need to complete remote KCCQ	To assist participant with management of the electronic PRO assessment device at home	Non-substantial
Section 2.3.1 (Risk Assessment)	Updates to number of participants with events of maculopapular rash	Updated in line with latest data for completed Phase 1 studies	Non-substantial
Section 3.1 (Objectives and Endpoints: Part A Table 4: Objectives and Endpoints - Safety)	Observed value and absolute change from baseline values over time for ECG measurements removed and replaced with investigator evaluation	Correction as observed values are not being collected only investigator evaluation	Non-substantial
Section 3.1 (Objectives and Endpoints: Part A Table 4: Objectives and Endpoints - Tertiary/ Exploratory)	Removal of objectives and endpoints related to: • pVO_2 • Activity monitor • Holter patch • 1MSTST • Collection of pulse oximeter data	Simplification of the CSP	Non-substantial
Section 3.1 (Objectives and Endpoints: Part A Table 4: Objectives and Endpoints - Tertiary/ Exploratory)	Addition of urine to objective wording for exploratory analysis of biomarkers	To align with update to endpoints	Non-substantial
Section 3.1 (Objectives and Endpoints: Part A Table 4: Objectives and Endpoints - Tertiary/ Exploratory)	Removal of insulin from endpoints for exploratory analysis of biomarkers	Simplification of the CSP	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 3.1 (Objectives and Endpoints: Part A Table 4: Objectives and Endpoints - Tertiary/ Exploratory)	Addition of UACR to endpoints for exploratory analysis of biomarkers	Addition of UACR as a biomarker of endothelial dysfunction for prognostic evaluation in the study population	Non-substantial
Section 3.2 (Objectives and Endpoints: Part B Table 5: Objectives and Endpoints - Safety)	Observed value and absolute change from baseline values over time for ECG measurements removed and replaced with investigator evaluation.	Correction as observed values are not being collected only investigator evaluation	Non-substantial
Section 3.2 (Objectives and Endpoints: Part B Table 5: Objectives and Endpoints - Tertiary/ Exploratory)	Removal of objective and endpoint related to activity monitor	Simplification of the CSP	Non-substantial
Section 4.3 (Justification for Dose)	Updates to exposure in Phase 1 studies and number of participants with events of maculopapular rash	Updated in line with latest data for completed Phase 1 studies	Non-substantial
Section 5.1 (Inclusion Criterion 2)	Rewording of text in relation of signs and symptoms of HF to align with Appendix G.	Text related to signs of symptoms of HF clarified to align with Appendix G.	Non-substantial
Section 5.1 (Inclusion Criterion 2)	Removal of text relating to participant use of an oral diuretic prior to study entry	For the removal of text related to use of oral diuretic. Site clinicians to make the clinical diagnosis of HF. The degree of congestion and/or diuretic use does not impact the scientific rationale for the study, nor the anticipated effect of AZD4831	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 5.1 (Inclusion Criterion 3)	Removal of text in relation to documenting LVEF > 40% within 12 months prior to Screening and added LVEF should be > 40% at Screening Visit 1	Simplification of the CSP as the LVEF is confirmed on the echocardiogram performed at the screening visit and read through central imaging core laboratory this historical confirmation is deemed as not necessary	Non-substantial
Section 5.1 (Inclusion Criterion 13)	Removal of optional informed consent collection for retinal scan	Retinal scans are no longer being performed in this study	Non-substantial
Section 5.1 (Inclusion Criterion 14)	Removal of optional informed consent collection for Paxgene RNA analysis	Paxgene RNA analysis is no longer being performed in this study	Non-substantial
Section 5.2 (Exclusion Criterion 6)	Removal of method of assessment sub bullets	To improve clarity the additional sub bullets were removed as these do not assist with the assessment of exercise capacity.	Non-substantial
Section 5.2 (Exclusion Criterion 8)	Change of text from cardiac to cardiovascular and expansion of text to include aortic aneurysm surgery, etc	Typographical update from cardiac to cardiovascular, and for clarity further examples of planned cardiovascular procedures given	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 5.2 (Exclusion Criterion 23)	Removal of bullet related to signs and symptoms consistent with COVID-19	Bullet removed as the examples for signs and symptoms cover conditions other than COVID-19 which are not always exclusionary therefore this added bullet is not deemed necessary and is covered in the first line of the exclusion.	Non-substantial
Section 6.1.2 (Medical Devices)	Section removed	DMS MyPatch, Masimo MightySat and Actigraph Centrepoint Insight Watch no longer being used due to simplification of the protocol. Section therefore no longer applicable	Non-substantial
Section 8 (Study Assessments and Procedures)	Total blood volumes collected on study revised to: • 318 mL (from 420 mL) for Part A • 194 mL (from 250 mL) for Part B	In line with reduction and removal of samples	Non-substantial
Section 8.1.1 (Patient Reported Outcomes)	Wording added that PRO assessments completed at home could be removed for Part B if not supported from the Part A Week 16 interim analysis. Removed reference to 1MSTST Language added to permit the omission of the at home collection of the KCCQ. Participant inability to use the electronic device at home for specified reasons will not preclude their participation in the study	To allow for removal of the remote collection of KCCQ for Part B 1MSTST removed at this amendment, therefore no longer applicable To allow for instances where participants find they are not able, or comfortable, to use the electrical device at home	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
	Text added to indicate that telephone contact will be made by the site to remind participants of the need to complete remote KCCQ	To assist participant with management of the electronic PRO assessment device at home	Non-substantial
Section 8.1.1.3 (Patient Global Impression of Severity in Walking Difficulties [Part A only])	Removed reference to 1MSTST	1MSTST removed at this amendment, therefore no longer applicable	Non-substantial
Section 8.1.1.4 (Patient Rating of Dyspnoea, Acute Version)	Removed reference to 1MSTST	1MSTST removed at this amendment, therefore no longer applicable	Non-substantial
Section 8.1.3 (6-Minute Walk Test)	Reference to 1MSTST being done after 6MWT removed	1MSTST removed at this amendment, therefore no longer applicable	Non-substantial
Section 8.1.4 (Echocardiography)	Text added to permit > 7 days for a repeat echocardiogram assessment following the screening echocardiogram. Repeat assessment to be completed prior to randomisation (Visit 3)	To allow greater flexibility with repeat echocardiogram scheduling at Screening	Non-substantial
Section 8.1.5 (Peak VO_2 Cardiopulmonary Exercise Test [Part A only])	Section removed	Simplification of the CSP	Non-substantial
Section 8.1.7 (Activity Monitoring)	Section removed	Simplification of the CSP	Non-substantial
Section 8.1.8 (1-Minute Sit-to-stand Test [Part A only])	Section removed	Simplification of the CSP	Non-substantial
Section 8.1.9 (Holter Patch [Part A only])	Section removed	Simplification of the CSP	Non-substantial
Section 8.1.10 (Retinal Scan [Part A only])	Section removed	Simplification of the CSP	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 8.2.1 (Physical Examinations)	Part B Visit 10 changed to Visit 9 BMI calculation included	Visit 8 removed from CSP (collection of activity monitor) – visit numbers updated accordingly For clarity	Non-substantial
Section 8.2.2 (Vital Signs)	Clarified that for Part A, the repeated supine blood pressure measurement at Visit 3 can also be used as the pre-dose supine measurement for the orthostatic test as long as the required conditions are met	To reduce the number of repeated blood pressure measurements at Visit 3	Non-substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments)	Indicated that ANCA samples may be collected if clinically indicated	For clarification	Non-substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments)	Removal of complement sample collection from Table 8 Text relating to blood sample collection and measurement for ANCA and complement (taken at Week 4, Week 12, Week 24, Week 36, Week 52 Follow-up for Part A and Week 4 and Week 28 Follow-up for Part B) removed as these samples are no longer being taken	Simplification of the CSP	Non-substantial
Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE Information)	Part B Visit 11 changed to Visit 10	Visit 8 removed from CSP (collection of activity monitor) – visit numbers updated accordingly	Non-substantial
Section 8.3.10 (Medical Device Deficiencies)	Section removed	Medical devices no longer being used in the study. Section no longer applicable	Non-substantial.
Section 8.5.1 (Pharmacokinetics)	Part B Visit 10 changed to Visit 9	Visit 8 removed from CSP (collection of activity monitor) – visit numbers updated accordingly	Non-substantial

Section number and name	Description of changes	Brief rationale	Substantial/ non-substantial
Section 8.6.2 (Collection of Mandatory Samples for Exploratory Biomarker Analysis)	Removal of insulin from endpoints for exploratory analysis of biomarkers	Simplification of the CSP	Non-substantial
Section 8.6.2 (Collection of Mandatory Samples for Exploratory Biomarker Analysis)	Addition of UACR to endpoints for exploratory analysis of biomarkers	Addition of UACR as a biomarker of endothelial dysfunction for prognostic evaluation in the study population	Non-substantial
Section 8.6.6 (Optional Collection of Paxgene Blood Sample for RNA Analysis [Part A only])	Section removed	Paxgene RNA analysis is no longer being performed in this study	Non-substantial
Section 9.4.3 (Safety; Electrocardiograms)	Section updated as ECG data will be investigator evaluation rather than individual ECG values	Correction as observed values are not being collected only investigator evaluation	Non-substantial
Appendix A 5 Committees Structure	Addition of a further external member	Request of French regulatory authority	Non-substantial
Appendix Q (Protocol Amendment History)	Details of Amendment 1 moved to this section	Change in line with CSP template requirements	Non-substantial

1MSTST, 1-minute sit-to-stand test; 6MWT, 6-minute walk test; AE, adverse event; ANCA, anti-neutrophil cytoplasmic antibody; BMI, body mass index; COVID-19, coronavirus disease 2019; CPET, cardiopulmonary exercise test; CSP, clinical study protocol; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricle ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; PRO, patient reported outcome; pVO_2, peak volume of oxygen consumption; RNA, ribonucleic acid; SAE, serious adverse event; UACR, urinary albumin-to-creatinine ratio.

Amendment 1 (25 May 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

To provide clarifications on various points, to remove unnecessary tests, and include additional safety testing based on regulatory feedback.

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Urine sample for biomarker analysis line added for sample that is sent to central laboratory.	To add clarity to distinguish between urine sample tested at site and sample tested by central laboratory for uric acid.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A and Table 1 Part B)	Pregnancy testing removed.	As women of childbearing potential are excluded from the study pregnancy testing is not considered necessary.	Substantial
Section 1.2 (Study Design Part A) Section 1.3 (Schedule of Activities Table 1 Part A and related footnotes a and g)	Removal of remote 1MSTST measurement.	Reduce complexity of study.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	As Visit 5 now only covers a telephone call to check for AEs, timing been changed from 11 weeks post-randomisation to 8 weeks post-randomisation.	To check AEs midway between Visit 4 and 6.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Removal of assessment of AEs at Visit 2 and Visit 7.	In line with removal of 1MSTST, site no longer contacting the participant at this visit.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote e related to orthostatic hypotension updated to include measurement 1-2 hours after the first dose of AZD4831.	Added in line with recommendations from FDA.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote g updated to remove reference to site reminding participant to wear activity monitor whilst doing the 1MSTST at home.	Text removed as not applicable.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote h updated to modify the timepoints from 0.5-1 hours and 1-3 hours to 0.5-1.5 hours and 1.5-3 hours post dose timepoints for PK at Visit 6 and to clarify that when approximately 20% of the participants having this assessment have been reached no further participants need undergo the extra PK sampling.	To modify the timepoints and reduce participant burden by limiting the number of participants undergoing extra PK assessments post dose.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote i updated to clarify that urine sample at Visit 3, Visit 8 and Visit 11 is sent to central laboratory.	To distinguish between urine sample tested at site and sample tested by central laboratory for uric acid.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote j text added specifying that Met-haemoglobin is performed at sites that have the facility to conduct this test.	To clarify as not all sites have the facilities to conduct this test.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A and Table 1 Part B)	Footnote l added to clarify that screening echocardiogram can be performed on a different day to Screening Visit 1 if not possible to schedule on the same day but must be done as soon as possible after Screening Visit 1 ie, within 1-2 days.	To accommodate for potential scheduling difficulties.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part A)	Footnote n updated to clarify that the patch be placed on participant after the echocardiogram.	As the patch will interfere with conducting the echocardiogram the patch should be placed on the participant after the echocardiogram.	Non-substantial
Section 1.3 (Schedule of Activities Table 1 Part B)	AE check added at Visit 8.	Participant would be coming to clinic at this visit, so AE check added.	Non-substantial
Section 3 (Objectives and Endpoints Part A, Table 4)	Text regarding remote 1MSTST removed.	In line with removal of remote 1MSTST.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 3 (Objectives and Endpoints Part A, Table 4 and Part B, Table 5)	Specified comparison with placebo for tertiary/exploratory objective on NHYA class.	For clarity.	Non-substantial
Section 5.1 (Inclusion Criteria)	Section on informed consent updated to include optional collection of paxgene blood sample for RNA analysis.	Updated as collection of paxgene blood sample for RNA analysis is also an optional consent.	Non-substantial
Section 5.2 (Exclusion Criteria)	Exclusion Criterion 12 updated to clarify cardiomyopathies.	To add clarity to criteria of cardiomyopathies.	Non-substantial
Section 5.2 (Exclusion Criteria)	Exclusion Criterion 17 updated to include any known and ongoing Hepatitis B or C.	To add clarity to the exclusion of chronic infectious liver disease.	Non-substantial
Section 5.2 (Exclusion Criteria)	Exclusion Criterion 21 updated to prior history of drug or alcohol abuse to be abuse likely to impact participant safety or compliance with study procedures as judged by the investigator.	To add clarity to the criteria of prior history.	Non-substantial
Section 5.3.1 (Meals and Dietary Restrictions)	Text added that study intervention can be taken with or without food.	To clarify that study intervention can be taken with or without food.	Non-substantial
Section 8.1.1.4 (Patient Rating of Dyspnoea, Acute Version)	Reference at home removed.	In line with removal of remote 1MSTST.	Non-substantial
Section 8.1.8 (1-Minute Sit-to-Stand Test Part A only)	Text removed regarding assessment at home.	In line with removal of remote 1MSTST to reduce complexity of the study.	Non-substantial
Section 8.2.2 (Vital Signs)	Assessment of orthostatic vitals at 1-2 hours after the first dose of AZD4831 added.	Added in line with recommendations from FDA.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 8.2.2 (Vital Signs)	Cut-offs for change in systolic and diastolic blood pressure to diagnose orthostatic hypotension based on baseline systolic blood pressure updated to be definition of orthostatic hypotension a drop of ≥ 20 mmHg of systolic blood pressure or ≥ 10 mmHg independent of the baseline blood pressure.	Added in line with recommendations from FDA.	Non-substantial
Section 8.2.2 (Vital Signs)	Text added regarding participants with orthostatic hypotension.	Added in line with recommendations from FDA.	Non-substantial
Section 8.2.2 (Vital Signs)	Instructions added regarding recording of symptoms of dizziness or light headedness.	Added in line with recommendations from FDA.	Non-substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments [Table 8])	Table updated to remove reference to uric acid sample as this has now been added to Schedule of Activities table. Reference to pregnancy testing removed in table.	To add clarity to distinguish between urine sample tested at site and sample tested by central laboratory. To reflect update of removal or pregnancy testing.	Non-substantial
Section 8.2.4 (Clinical Safety Laboratory Assessments)	Text added to clarify that the blood samples for ANCA and complement taken at Week 4, Week 12, Week 24, Week 36, Week 52 follow-up for Part A and Week 4 and Week 28 Follow-up for Part B will be collected and only be measured if the resulting analyses are deemed to be useful to further evaluation of AZD4831 based on emerging study data.	To add clarity samples will be collected at the highlighted timepoints but not measured unless deemed to be useful for further evaluation of AZD4831. These samples are still useful to be collected if needed based on emerging safety data.	Non-substantial
Section 8.3.8.1 (Maternal Exposure)	Congenital abnormality changed to congenital anomaly.	To meet regulatory requirements on good pharmacovigilance practices.	Non-substantial
Section 8.3.8.1 (Maternal Exposure)	Wording “When the eCRF module is used include the following” removed.	Text not required as authoring instruction.	Non-substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 9.4.2.1 (Primary Endpoint(s))	Text updated regarding primary objectives related estimands.	To be more specific.	Non-substantial
Section 3	Minor edits to statistics wording	To correct typographical errors.	Non-substantial
Appendix O (Covid-19 specifics)	Wording added that study intervention may be delivered direct to participant if appropriate and via Sponsor approved courier service.	Added as potential mitigation for Covid-19.	Non-substantial

1MSTST, 1-minute sit-to-stand test; AE, adverse event; ANCA, anti-neutrophil cytoplasmic antibody; Covid-19, coronavirus disease 2019; eCRF, electronic case report form; FDA, Food and Drug Administration; PK, pharmacokinetics.

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