Clinical Study Protocol	
Drug Substance	AZD4831
Study Code	D6580C00003
Version	4.0
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A randomized, double blind, placebo-controlled, parallel group, multicentre, phase 2a study to assess target engagement, safety and tolerability of AZD4831 in patients with Heart Failure with preserved Ejection Fraction (HFpEF)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2018-002895-42

VERSION HISTORY

Version 1.0 6 July 2018
This is the first version of the clinical study protocol
Version 2.0 27 November 2018 Changes to the clinical study protocol are summarized below
Non-substantial amendment to the protocol: Table 4 in section 6.5 is updated to give examples of potent CYP3A4 inhibitors and inducers. A comment asking Investigators to refer to concomitant medications SmPCs for further or more detailed information, was added below the Table 4.
Version 3.0 12 March 2019 Changes to the clinical study protocol are summarized below
Visit window for visit 1 is updated. Subjects may enter a screening period up to 28 days prior to visit 2. If visit 1 is performed more than 14 days prior to visit 2, all assessments except blood and urine sampling should be completed at that visit. Blood and urine samples related to visit 1 must be taken within 14 to 0 days prior to visit 2 to ensure patient eligibility. The following sections of the Clinical study protocol (CSP) have been updated to reflect this change: 1.1 Schedule of Activities, 1.2 Synopsis, 4.1 Overall Design It was previously stated that *recruitment* to part B may proceed only after the evaluation of the interim analysis. In this version it is changed to that *randomization* may proceed after evaluation of the interim analysis. This will enable the site to enroll but not randomize patients to part B before the evaluation of the interim analysis is final. The following sections of the CSP have been updated to reflect this change: 1.2 Synopsis, 4.1 Overall Design Clarification that start of interim analysis should be initiated once all subjects in part A have been treated for *approximately* 30 days. The following sections of the CSP have been updated to reflect this change: 1.2 Synopsis, 4.1 Overall Design, 9.5 Interim Analyses.

The inclusion criteria 5 was updated to BMI 18- 40kg/m^2 to increase the potential population to be included.
The following section of the CSP have been updated to reflect this change: 5.1 Inclusion criteria

Exclusion criteria 23 is updated to clarify this relates to patients with known positive HIV, hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody, at screening visit. The following section of the CSP have been updated to reflect this change: 5.2 Exclusion Criteria

Clarification regarding PK analysis. PK concentrations may be assessed during the study for evaluation of the exposure levels.
The following sections of the CSP have been updated to reflect this change: 8.5.1 Determination of drug concentration

Clarification that PK samples at visit 7 should be taken at predose, 0.5 -1h, 1-3h and >3 h after dose, not to limit the last sample to be taken within 5 hours as previously stated.
The following section of the CSP have been updated to reflect this change: 1.1 Schedule of Activities

The blood volume for genetic sample is updated to be aligned with the Laboratory Manual and the Informed Consent Form. Volume decreased from 10mL to 6mL.
The following section of the CSP have been updated to reflect this change: 8.7.1 Optional exploratory genetic sample

Clarification added to the hypothesis for the first secondary efficacy endpoint CFVR to reflect the sample size calculation for CFVR.
The following sections of the CSP have been updated to reflect this change: 1.2 Synopsis, 9.4.1 Efficacy analyses

Clarification added regarding analysis of TE Biomarker as requested from the authorities in the Netherlands.
The following section of the CSP have been updated to reflect this change: 9.2 Sample size determination

Clarification is added regarding analysis of prematurely discontinued patients.
The following section of the CSP have been updated to reflect this change: 9.3.1 Full analysis set

Clarification that the primary and secondary efficacy variables are measured as percent change from baseline to end of treatment, and not to end of study.

The following sections of the CSP have been updated to reflect this change: 9.4 Statistical analyses, 9.4.1 Efficacy analyses Appendix E wording has been updated in order to clarify the process of Potential Hy's Law and Hy's Law cases reporting in accordance with the FDA Guidance for Industry (issued July 2009) 'Drug induced liver injury: Premarketing clinical evaluation'. The following section of the CSP have been updated to reflect this change: Appendix E
Version 4.0 9 January 2020 Changes to the clinical study protocol are summarized below.
Exclusion criteria 1 is updated to decrease eGFR from 45 to 30 ml/min/1.73m2, at screening visit. The following section of the CSP has been updated to reflect this change: 5.2 Exclusion criteria. Justification of change: Metabolism of AZD4831contributes to the overall elimination as several metabolites were evident in the SAD (D6580C00001) and the MAD (D6580C00004) study. However, elimination is also dependent on renal function since ≥30 % of the dose was recovered in urine after oral dosing in healthy subjects with normal renal function (SAD and MAD). Moreover, linear regression analysis of the elimination (CL/F) vs. eGFR data obtained from SAD, MAD and the current study (D6580C00003, eGFR above 45 mL/min/1.73m2) confirmed the correlation between elimination of AZD4831 and renal function. The predicted exposure in a typical patient with an eGFR of 30 mL/min/1.73m2 is predicted to be 2.0 times higher than a typical healthy subject with an eGFR of 107 mL/min/1.73m2 (median eGFR in SAD and MAD). Corresponding value for a typical patient with an eGFR of 45 ml/min/1.73m2 is predicted to be 1.7 times higher compared to a healthy subject with an eGFR of 107 ml/min/1.73m2. This predicted difference in exposure between a patient with an eGFR of 30 mL/min/1.73m2 vs a patient with an eGFR of 45 mL/min/1.73m2 is considered small. Since most of the patients will have reduced renal function, and the predicted difference in exposure is small, the exclusion criterion on eGFR is changed from 45 mL/min/1.73m2 to 30 mL/min/1.73m2. Exclusion criteria 20 is updated to: Patients with uncontrolled or clinically significant thyroid disease as judged by the investigator. The following sections of the CSP have been updated to reflect this change: 2.2. Background. In patients with heart failure, low T3 levels have been associated with myocardial fibrosis and abnormalities in myocardial perfusion and metabolism. The low T3 syndrome, defined as a low T3 level with levels of TSH and FT4 in the reference range, is present in 20% to 30% of patients with heart failure.

5.2 Exclusion criteria. Justification of change: Clinical safety margins have been calculated based on exposures at the NOELs for changes in TSH levels in the 3-month rat and dog toxicology studies. At the NOELs, the mean AUC values for total AZD4831 achieved in the 3-month dog and rat toxicology studies were 69 umol*h/L and 173 umol*h/L, respectively. After repeated dosing in the MAD study, the mean AUC for the [redacted] dose level was 1.45 umol*h/L, which is approximately 48 and 119 times lower than the respective toxicology study NOEL exposures.

In addition, blinded data for the TSH, T3, T4 hormone level dynamics was assessed for 26 patients. There were no clinically significant changes, meaningful deviations or trends identified. Therefore, the established nonclinical safety margins in conjunction with the ability to readily monitor for thyroid function in the clinic support the revised inclusion/exclusion criteria for thyroid function.

Exclusion criteria 3 is updated with a clarification: Any ongoing skin disorder, history of or ongoing clinically significant allergy/hypersensitivity. The following section of the CSP has been updated to reflect this change: 5.2 Exclusion criteria.

Table 6 - Safety laboratory assessments is updated with the addition of TSH, T3 and T4 sampling at visit 7.

Clarification that *approximately* 96 randomized patients will be included in the study and addition of *approximate* 59 remaining patients in Part B.

Section 4.1, Overall design, general description of visits. Visit 1 (enrollment) and Visit 2 (randomization) are updated to clarify in case visit 1 and visit 2 occur at the same day, local lab results will enroll the patient, in case they meet the inclusion criteria. In case the central lab results are returned and do not meet the inclusion criteria, the patient will not be withdrawn.

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

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study of Assessments

	Visit 1[a, j]	Visit 2[a, j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8	Details in CSP section or Appendix
Description	**Enrollment**	**Randomization** [redacted]	**Part A** [redacted] **or** [redacted] **Part B**								**End of Treatment**	**Follow-up**	
Day from randomization	**-28 to 0**	**0**	**10**	**20**	**20**	**20**	**30**	**60**	**60**	**60**	**90**	**120**	
Visit window (in relation to randomization)		**Within 28 days from enrollment**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 3 days**	**+/-4 days**	**+/-4 days**	**+/-4 days**	**+2 days or – 7 days**	**+/-4 days**	
Informed consent	X												*Section 4.1, and Appendix A 3*
Informed consent for Genetic sampling (optional)	X												*Section 4.1 and 8.7*
Inclusion /exclusion criteria	X	X											*Section 5.1 and 5.2*
Alcohol, Drug of abuse and nicotine use	X												*Section 5.2*
Demography	X												*Section 4.1*
Medical & Surgical history	X												*Section 4.1*
Pregnancy test (serum or urine, females only)	X												*Section 5.2*
Randomization		X											*Section 6.3*

	Visit 1[a, j]	Visit 2[a, j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8	Details in CSP section or Appendix
Description	**Enrollment**	**Randomization** [redacted]	[redacted] – **Part A** [redacted] **or** [redacted] – **Part B**								**End of Treatment**	**Follow-up**	
Day from randomization	**-28 to 0**	**0**	**10**	**20**	**20**	**20**	**30**	**60**	**60**	**60**	**90**	**120**	
Visit window (in relation to randomization)		**Within 28 days from enrollment**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 3 days**	**+/-4 days**	**+/-4 days**	**+/-4 days**	**+2 days or – 7 days**	**+/-4 days**	
IP dispensed		X	X				X						*Section 6.1.1*
IP returned and accountability checked			X				X				X		*Section 6.4*
IP intake at site		X	X	X		X[c]	X	X		X[c]	X		*Section 4.1*
Patient Diary Card hand out		X											*Section 6.4*
Patient Diary Card review by site staff			X	X		X	X	X		X	X		*Section 6.4*
Optional Genetic Sampling		X											*Section 8.7*
Physical examination[d]	X	X	X	X			X	X			X	X	*Section 8.2.2*
Supine BP and pulse rate	X	X	X	X		X	X	X		X	X	X	*Section 8.2.4*
Height	X												*Section 8.2.4*
Weight	X	X	X	X		X	X	X		X	X		*Section 8.2.4*
Body temperature	X	X		X		X	X	X		X	X		*Section 8.2.4*
Digital 12 lead ECG	X	X	X	X			X	X			X	X	*Section8.2.5*
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	*Section 6.5*

	Visit 1[a, j]	Visit 2[a, j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8	Details in CSP section or Appendix
Description	**Enrollment**	**Randomization** [redacted]	[redacted] – **Part A** [redacted] **or** [redacted] – **Part B**								**End of Treatment**	**Follow-up**	
Day from randomization	**-28 to 0**	**0**	**10**	**20**	**20**	**20**	**30**	**60**	**60**	**60**	**90**	**120**	
Visit window (in relation to randomization)		**Within 28 days from enrollment**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 3 days**	**+/-4 days**	**+/-4 days**	**+/-4 days**	**+2 days or – 7 days**	**+/-4 days**	
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	*Section 8.3*
Safety laboratory assessment	X[j]	X	X	X[f]		X[f]	X	X[f]		X[f]	X	X	*Section 8.2.1, Table 6*
Serology	X												*Table 7*
PK sampling for AZD4831			X (pre-dose only)	X (pre-dose only)		X (pre-dose only)	X (pre-dose only)	X (pre-dose only)		X (pre-dose only)	X[g]	X	*Section 8.5*
TE biomarker		X	X				X				X		*Section 8.1.1*
NT-ProBNP/BNP	X[h, j]	X					X				X		*Table 5*
Blood sampling for Lipid status		X					X				X		*Table 5*
Other laboratory samples		X					X				X		*Table 5*
Collection of exploratory samples		X		X		X	X	X		X	X	X	*Section 8.8*
Endogenous MPO mass activity measurement		X					X				X		*Section 8.8*
CFVR measurement		X									X		*Section 8.1.2.2*

	Visit 1[a, j]	Visit 2[a, j]	Visit 3	Visit 4[b] (if at site)	Visit 4[b] (if TC)	Visit 4[b] (if at home)	Visit 5	Visit 6[b] (if at site)	Visit 6[b] (if TC)	Visit 6[b] (if at home)	Visit 7	Visit 8	Details in CSP section or Appendix
Description	**Enrollment**	**Randomization** [redacted]	[redacted] – **Part A** [redacted] **or** [redacted] – **Part B**								**End of Treatment**	**Follow-up**	
Day from randomization	**-28 to 0**	**0**	**10**	**20**	**20**	**20**	**30**	**60**	**60**	**60**	**90**	**120**	
Visit window (in relation to randomization)		**Within 28 days from enrollment**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 2 days**	**+/- 3 days**	**+/-4 days**	**+/-4 days**	**+/-4 days**	**+2 days or – 7 days**	**+/-4 days**	
Echocardio-graphy	X[i]	X					X				X		*Section 8.1.2.1*
EndoPAT™ test		X					X				X		*Section 8.1.2.4*
PWV/PWA		X					X				X		*Section 8.1.2.3*
6MWT		X					X				X		*Section 8.1.2.5*
KCCQ		X					X				X	X	*Section 8.9.1*
Patient arrives fasting to visit		X					X				X		*Section 5.4.1*

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

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

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

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

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

[f] A modified safety sample panel will be taken at visit 4 and visit 6, see Table 6

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

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

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

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

1.2 Synopsis

Protocol Title:

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

Short Title:

A phase 2a study to assess target engagement, safety and tolerability of AZD4831 in patients with HFpEF.

Rationale:

The primary objective of this study is to evaluate the target engagement of AZD4831 by measuring myeloperoxidase (MPO) specific activity in plasma following ex vivo stimulation of fresh blood samples with zymosan, in patients with heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). Secondly, to evaluate the safety and tolerability of AZD4831 in patients with HFpEF and HFmrEF and the incidence of maculopapular rash grade 3. In addition, the effect of AZD4831 on Coronary Flow Velocity Reserve (CFVR) as a measure of myocardial microvascular function will be evaluated.

For the current moment, there are no available point of care assays for the on-site screen testing enabling the selection of patients with high levels of MPO. There are no known potential surrogate markers offer enough evidence of linkage with the MPO levels. Consequently, separate exploratory objective will be focused on the assessment of all secondary/exploratory outcomes in the sub-group of patients with elevated MPO-pathway biomarkers.

The study will be conducted in adaptive design manner. Part A will establish if the safety and tolerability profile, and target engagement are acceptable to continue into Part B of the study. Pending observed target engagement in Part A, there is also a possibility to adjust the dose for patients randomized in Part B which will mainly focus on efficacy and effect on target engagement versus placebo. The result of the study treatment will provide a more complete AZD4831 safety and tolerability profile and will facilitate the scientific and clinical basis for further investigation of AZD4831 in improving cardiovascular mortality and morbidity on top of standard of care (SoC) in HFmrEF and HFpEF population. The treatment duration for this study is 90 days, which should be sufficient for the reliable assessment of secondary objective.

Objectives and Endpoints	
Primary Objective:	***Endpoint/Variable:***
To compare the effect of AZD4831 to placebo on target engagement	Change from baseline in target engagement marker, defined as *ex vivo* zymosan stimulated MPO specific activity (MPO activity divided by MPO protein mass), normalised. Hereafter referred as TE biomarker throughout the CSP
Secondary Objective:	***Endpoint/Variable:***
To compare the effect of AZD4831 to placebo on coronary flow velocity reserve (CFVR)	Change from baseline in CFVR measured in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE).
To compare the effect of AZD4831 to placebo on 6 minutes walking test (6MWT)	Change from baseline in Walking distance
To assess the pharmacokinetics (PK) of AZD4831 after repeated dosing	Standard model population pharmacokinetic (PK) parameters to be reported in a separate report.
Safety Objectives	***Endpoint/Variable:***
To assess safety and tolerability of AZD4831	– Adverse Events/Serious Adverse Events (AEs/SAEs) including incidence of maculopapular rash grade 3 – Vital signs – Clinical chemistry/ haematology/ urinalysis parameters – Electrocardiogram (ECG) assessments
Exploratory:	***Endpoint/Variable:***
To explore the effect of AZD4831 on myocardial strain, measured as global longitudinal strain (GLS) compared to placebo	Change from baseline in GLS as measured by strain imaging echocardiography

To explore the effect of AZD4831 on right ventricular free wall longitudinal strain compared to placebo	Change from baseline in right ventricular free wall longitudinal strain measured by strain imaging echocardiography
To explore the effect of AZD4831 on left atrium reservoir strain compared to placebo	Change from baseline in left atrium reservoir strain measured by strain imaging echocardiography
To explore the effect of AZD4831 on diastolic function (measured as ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e')) compared to placebo	Change from baseline in E/e' as measured by standard echocardiography
To explore the effect of AZD4831 on peripheral endothelial function compared to placebo	Change from baseline in Reactive hyperemic index (RHI)
To explore the effect of AZD4831 on pulse wave velocity (PWV) and Pulse Wave Analysis (PWA) compared to placebo	Change from baseline in PWV and PWA
To explore the effect of AZD4831 on NT-proBNP compared to placebo	Change from baseline in NT-proBNP values
To explore the effect of AZD4831 on changes in health-related Quality of Life (QoL) compared to placebo	Change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, with specific focus on physical function domain
To explore the effect of AZD4831 on left atrium volume index (LAVI) compared to placebo	Change from baseline in LAVI
To explore the effect of AZD4831 on MPO-related biomarkers compared to placebo	Change from baseline in MPO- related biomarkers
To collect and store samples for potential future exploratory research aimed at exploring biomarkers involved in PK, pharmacodynamic (PD), efficacy, safety and tolerability related to HFpEF and AZD4831 treatment.	Exploratory biomarker analysis in plasma, serum and urine

To explore all secondary and exploratory objectives in patients with elevated MPO-pathway biomarkers	Corresponding variables for secondary and exploratory endpoints
Optional: To collect and store samples for potential future exploratory genetic research aimed at e.g. identifying/exploring genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD4831 treatment	

Overall design:

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

Part A:

At visit 1 the patients will be checked for eligibility and enrolled to the study. 37 patients will be randomized at visit 2 in a 2:1 ratio to once daily dosing of AZD4831 or matching placebo. The patients will be dosed the first 10 days (until visit 3) with a starting dose of [redacted] once daily AZD4831 or matching placebo. After 10 days, at visit 3, the dose will be increased to [redacted] AZD4831 or matching placebo and patients will be treated for another 20 days (visit 4 and visit 5). When all 37 patients have been treated for approximately 30 days an interim analysis will follow but the 37 patients included in part A will continue the treatment at [redacted] AZD4831 or matching placebo once daily for another 60 days until stop of treatment and complete the next visit approximately every 30 days for visit 6 and visit 7. After the stop of treatment patients will be followed-up (visit 8) after approximately 30 days.

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

Part B:

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

NB: At all visits, patients will be instructed to contact the investigator immediately, if rash has developed at any time point of the study. Patients will be recommended to make an acceptable quality self-photo of skin affected with rash. If any patient develops a confirmed generalised maculopapular rash grade 3, throat tightness or angioedema at any time during the study, the relevant site investigator should immediately stop the study drug and arrange appropriate medical consultation to provide relevant treatment. Patient should visit the site for an un-scheduled visit (End-of Treatment visit = Visit 7).

During visit at site, if generalised maculopapular rash grade 3 is suspected, Investigator will make a quality photo(s) of patient's skin affected with rash, acceptable for the evaluation of rash according to guidance provided in Appendix B9. These photo(s) should be also provided to the AstraZeneca Safety Committee.

If the prespecified number of patients discontinues due to maculopapular rash grade 3 during Part A the dose for all the subsequently randomized patients in Part A may be adjusted or study may be stopped.

Study Period:

Estimated date of first patient enrolled: November 2018
Estimated date of last patient completed: Q2 2020

Number of Patients:

Approximately 150 patients will be enrolled to achieve approximately 96 randomized patients.

Treatments and treatment duration:

All patients will be treated once daily with AZD4831 or placebo for in total approximately 90 days.

In part A the first 37 patients will be treated for approximately 10 days with a starting dose at [redacted] AZD4831 or matching placebo once daily. After 10 days the dose will be increased to [redacted] AZD4831 or matching placebo once daily for approximately 80 days. When all patients in part A have been treated for approximately 30 days (visit 5) an interim analysis will be performed.

In part B the approximate 59 remaining patients will be treated for approximately 10 days with a starting dose at [redacted] AZD4831 or matching placebo once daily. After 10 days the dose may be maintained at [redacted] or increased to [redacted] or [redacted] AZD4831 or matching placebo once daily depending on the outcome of the interim analysis.

Safety Review Committee

A blinded Safety Review Committee (SRC) consisting of internal AstraZeneca (AZ) expertise will review safety data related to rash on an ongoing basis throughout the study and give input and recommendations to a Data Review Committee (DRC). For more information refer to SRC/DRC charter.

Data Review Committee

The number of patients who discontinue the study due to generalised maculopapular rash CTCAE grade 3 or higher will be continuously monitored by a Data Review Committee (DRC) and the study will be stopped if at any time the proportion of discontinued patients on AZD4831 is above a prespecified level. The DRC consists of internal AZ expertise.

The statistical monitoring will be described in the SRC/DRC charter that must be finalised before first patient in.

Statistical methods

The primary efficacy variable TE biomarker measure percent change from baseline to end of treatment in target engagement marker. The primary efficacy variable TE biomarker will test the null hypothesis of equality in TE biomarker comparing AZD4831 to placebo versus the alternative hypothesis of non-equality comparing AZD4831 to placebo at 5% two-sided significance level.

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

The primary efficacy variable TE biomarker and the first secondary efficacy variable CFVR will be analyzed using an ANCOVA model.

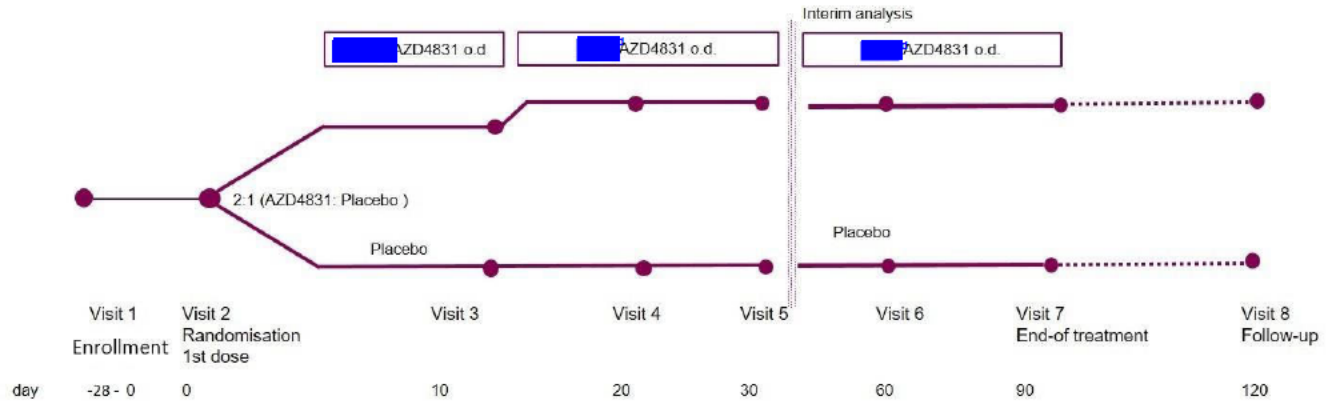
An interim analysis is planned after 37 patients, 25 on AZD4831 and 12 on placebo, have been treated for approximately 30 days in Part A. The interim analysis results will be used to decide on dose for Part B or to stop the study. Only patients treated with AZD4831 will be included in the analysis.

1.3 Scheme

The general study design is summarised in Figure 1.

Figure 1 Study design

Part A: 37 randomized patients



o.d = once daily

Part B: Approximately 59 randomized patients

o.d = once daily

2 INTRODUCTION

2.1 Study rationale

The primary objective of this study is to evaluate the target engagement of AZD4831, MPO inhibitor by measuring MPO specific activity in plasma following *ex vivo* stimulation of fresh blood samples with zymosan, in patients with HFpEF. MPO is known to influence vascular reactivity through consumption of endothelial Nitric Oxide (NO) under inflammatory conditions. Removing vascular MPO by using heparin and achieving a 45% reduction in MPO circulating levels has shown to significantly improve vascular function measured by Flow Mediated Dilation (Baldus et al 2006).

The objectives of this study are also to evaluate the safety and tolerability of AZD4831 in patients with HFpEF and HFmrEF and the incidence of maculopapular rash grade 3. In addition, to assess the effect of AZD4831 on CFVR as a measure of myocardial microvascular function. Impaired CFVR is known to reflect both macro and microvascular dysfunction and endothelial dysfunction. CFVR is defined as the ratio of maximal (stimulated) to baseline (resting) coronary blood flow (Gan et al 2013). While fractional flow reserve (FFR) reflects severity of focal coronary artery lesions, CFVR is a measure of the global coronary vascular function. Reduced CFVR has been shown to confer prognostic information for cardiovascular outcome in various conditions. Reduced CFVR is seen in patients with systemic inflammation and improves after immunomodulatory treatment. CFVR is also reduced in co-morbidities associated with HFpEF like diabetes, left ventricular hypertrophy (LVH) and hypertension. CFVR can be measured through a variety of invasive and non-invasive methods. TDE provides reliable measurements of CFVR in the distal or middle segment of the LAD coronary artery, using pulse wave Doppler. Compared to other methods it is relatively inexpensive, non-invasive and does not expose to radiation. The increase in blood flow can be induced with adenosine or dipyridamole, where adenosine has the advantage of being short-acting. Recently, this protocol has been successfully used in PROMIS-HFpEF study. The study provided evidences that coronary microvascular dysfunction is highly prevalent in HFpEF and it correlates with several key features of HFpEF, including disease severity, systemic endothelial dysfunction, as well as diastolic dysfunction (Shah SJ et al, 2018) For the current moment, there are no available point of care assays for the on-site screen testing enabling the selection of patients with high levels of MPO. There are no known potential surrogate markers offer enough evidence of linkage with the MPO levels. Consequently, separate exploratory objective will be focused on the assessment of all secondary/exploratory outcomes in the sub-group of patients with elevated MPO-pathway biomarkers.

Current study will evaluate safety and tolerability, efficacy and effect on target engagement in an adaptive design. Part A will establish if there is a satisfactory safety, tolerability and target engagement to continue into Part B of the study. Pending observed target engagement in Part A, there is also a possibility to adjust the dose for patients randomized in Part B. In Part B the

focus will mainly be on efficacy and effect on target engagement versus placebo. A placebo control arm in the trial will enable placebo-corrected analysis of safety and efficacy. In addition, the treatment duration of 3 months is expected to be of sufficient length to allow assessment of AZD4831 effect on CFVR and echocardiography parameters in HFpEF patients on top of long-term Standard of Care (SoC). The result of the study treatment will provide a more complete AZD4831 safety and tolerability profile and will facilitate the scientific and clinical basis for further investigation of AZD4831 in improving CV mortality and morbidity on top of SoC in HFpEF population.

Medical comorbidities including renal impairment, hypertension and diabetes mellitus are common in patients with HFpEF, consequently patients with these conditions will be included into this study. AZD4831 has not been studied in patients with renal impairment. AZD4831 is predominantly cleared via renal route, consequently, only patients with normal renal function and mild-moderate renal impairment (eGFR ≥30mL/min/1.73m2) will be included in the study, presuming that they have acceptable risk/benefit profile.

2.2 Background

Heart failure (HF) 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. HF is currently broadly divided into three categories based on the systolic function of the left ventricle: (1) HF with reduced ejection fraction (HFrEF; Left ventricle ejection fraction (LVEF) <40%), (2) HF with mid-range ejection fraction (HFmrEF; LVEF 40-49%); and (3) HF with preserved ejection fraction (HFpEF; LVEF ≥50%).

HFmrEF and HFpEF together 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.

HFpEF 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 hospitalizations per 1000 patient-years whereas in stable coronary disease it is 10-30 deaths and 5-10 hospitalizations 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 if successful of great public health impact (Kannan et al. 2018

Kannan L., Shaw P.A., Morley M.P., Brandimarto J, Fang J.C., Sweitzer N.K., Cappola T.P., Cappola A.R. Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes. Circ Heart Fail. 2018;11:e005266.

McMurray et al. 2012, Butler at al 2014).

In patients with heart failure, low T3 levels have been associated with myocardial fibrosis and abnormalities in myocardial perfusion and metabolism. The low T3 syndrome, defined as a low T3 level with levels of TSH and FT4 in the reference range, is present in 20% to 30% of patients with heart failure (Kannan et al. 2018).

A novel paradigm for HFpEF pathophysiology states that co-morbidities (age, renal disease, hypertension, obesity, 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 et al. 2013). This, in turn, can lead to both extracellular fibrosis and myocardial stiffness and reduced myocardial nitric oxide (NO) bioavailability and cyclic guanosine monophosphate (cGMP) 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 TDE-CFVR approach, Shah SJ et al provided recently the first robust evidence that coronary microvascular dysfunction is highly prevalent in HFpEF, diagnosed according to guidelines.

MPO 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 (Brennan et al 2003; Baldus et al 2003; Zhang R et al 2001) and MPO plasma levels predict outcome of cardiovascular disease. In chronic heart failure (HF), elevated plasma MPO levels are associated with more advanced HF. 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 anaesthetized 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). As published by Rudolph V et al 2010, MPO is also involved in structural remodelling of the myocardium, leading to an increased vulnerability to atrial fibrillation (Rudolph V et al 2010). Furthermore, in humans systemic MPO was increased in patients with established HFpEF and correlated with diastolic dysfunction independent of age and plasma B-type natriuretic peptide (Tang WH et al 2006).

Overall, recent evidence suggests that MPO may provide a mechanistic link between inflammation, oxidative stress, vascular dysfunction and impaired cardiac remodelling. It is thus hypothesized 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

AZD4831 is a first in class MPO inhibitor in development as a novel treatment for heart failure with preserved ejection fraction (HFpEF). Patients involved in the proposed study may derive some benefits from given treatment even though the duration of the treatment is limited up to 90 days. HFpEF 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.

AZD4831 has been administered to 59 healthy subjects in completed studies in single doses up to [redacted], and in repeated doses up to [redacted] for up to 14 days. There were no deaths or SAEs and all subjects except one completed the studies. The most common adverse events

were headache and generalized maculopapular rash. Dosing in [redacted] cohort in the Multiple Ascending Dose (MAD) study was stopped because of self-reported throat tightness in one subject that was considered intolerable by the Principal Investigator (PI) and SRC. This subject also had a more long-lasting rash of moderate intensity. Otherwise AZD4831has been well tolerated in healthy subjects. No clinically meaningful differences for changes over time in clinical laboratory tests, vital signs or ECGs were observed between subjects who received AZD4831 and those who received placebo. Preclinical safety studies have identified several potential risks including increment in liver enzymes and liver weights, elevation in thyroid stimulating hormone (TSH) and reduction in thyroxine (T4) levels, slight body weight loss and potential effects on heart rate and blood pressure. None of these findings were observed in the clinical studies performed to date. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of AZD4831 may be found in the Investigator's Brochure.

Based on knowledge of the mechanism of action, previous clinical experience and the preclinical safety studies the potential risks will be closely monitored and the patients will be withdrawn from Investigational Product (IP) if they present with rash grade 3, for definition of rash grade 3 see 7.1 No specific harms are anticipated from participating to this trial. Available preclinical and clinical data suggest that the subjects may benefit from participation in the study as inhibition of MPO activity may improve both coronary microvascular function and peripheral vascular function.

The essential imaging modality in the trial is cardiac ultrasound. The TDE with CFVR measurement has the advantage of being non-radioactive, non-invasive and utilizing equipment readily available in the departments of cardiology. The cardiac ultrasound examination itself does not involve any discomfort. To measure the ability to increase blood flow, intravenous adenosine will be used in connection to the ultrasound examination. Adenosine is approved as tool for cardiovascular examinations. It can provide a fast and transient (one minute) heat sensation and a slight chest discomfort. The most common adverse reactions are warmth, shortness of breath, flushing and headache. In rare cases, heart palpitations, nausea, anxiety or blurred vision may occur. Another rare condition is the risk for transient high degree Atrioventricular (AV) block and this risk is potentially higher in patients with bradycardia (heart rate< 50 beats/minute (bpm) and ongoing medication with e.g. beta-blocker and calcium-channel antagonist. Therefore, patients with AV block of second degree or higher or heart rate of less than 50bpm will be excluded from the present study. Under the medical attention provided in this trial, ultrasound CFVR measurement with adenosine infusion is not considered to pose a risk for the patients.

3 OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Objectives and Endpoints	
Primary Objective:	***Endpoint/Variable:***
To compare the effect of AZD4831 to placebo on target engagement	Change from baseline in target engagement marker, defined as *ex vivo* zymosan stimulated MPO specific activity (MPO activity divided by MPO protein mass), normalised. Hereafter referred as TE biomarker throughout the CSP
Secondary Objective:	***Endpoint/Variable:***
To compare the effect of AZD4831 to placebo on coronary flow velocity reserve (CFVR)	Change from baseline in CFVR measured in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE).
To compare the effect of AZD4831 to placebo on 6 minutes walking test (6MWT)	Change from baseline in Walking distance
To assess the pharmacokinetics (PK) of AZD4831 after repeated dosing	Standard model population pharmacokinetic (PK) parameters to be reported in a separate report.
Safety Objectives	***Endpoint/Variable:***
To assess safety and tolerability of AZD4831	– Adverse Events/Serious Adverse Events (AEs/SAEs) including incidence of maculopapular rash grade 3 – Vital signs – Clinical chemistry/ haematology/ urinalysis parameters – Electrocardiogram (ECG) assessments

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

To collect and store samples for potential future exploratory research aimed at exploring biomarkers involved in PK, pharmacodynamic (PD), efficacy, safety and tolerability related to HFpEF and AZD4831 treatment.	Exploratory biomarker analysis in plasma, serum and urine
To explore all secondary and exploratory objectives in patients with elevated MPO-pathway biomarkers	Corresponding variables for secondary and exploratory endpoints
Optional: To collect and store samples for potential future exploratory genetic research aimed at e.g. identifying/exploring genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD4831 treatment	

4 STUDY DESIGN

4.1 Overall design

For an overview of the study design see Figure 1. For details on treatments given during the study, see Section 6.1. For details on what is included in the efficacy and safety endpoints, see Section 3.

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

Part A:

At visit 1 the patients will be checked for eligibility and enrolled to the study. 37 patients will be randomized at visit 2 in a 2:1 ratio to once daily dosing of AZD4831 or matching placebo. The patients will be dosed the first 10 days (until visit 3) with a starting dose of [redacted] once daily AZD4831 or matching placebo. After 10 days, at visit 3, the dose will be increased to [redacted] AZD4831 or matching placebo and patients will be treated for another 20 days (visit 4 and visit 5). When all 37 patients have been treated for approximately 30 days an interim analysis will follow but the 37 patients included in part A will continue the treatment at [redacted] AZD4831 or matching placebo once daily for another 60 days until stop of treatment and complete the following visits approximately every 30 days for visit 6 and visit 7. After the stop of treatment patients will be followed-up (visit 8) after approximately 30 days.

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

Part B:

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

NB: At all visits, patients will be instructed to contact the investigator immediately, if rash has developed at any time point of the study. Patients will be recommended to make an acceptable quality self-photo of skin affected with rash. If any patient develops a confirmed generalised maculopapular rash grade 3, throat tightness or angioedema at any time during the study, the relevant site investigator should immediately stop the study drug and arrange appropriate medical consultation to provide relevant treatment. Patient should visit the site for an un-scheduled visit (End-of Treatment visit = Visit 7).

During visit at site, if generalised maculopapular rash grade 3 is suspected, Investigator will make quality photo(s) of patient's skin affected with rash, acceptable for the evaluation of rash

according to guidance provided in Appendix B9. These photo(s) will be also provided to the AstraZeneca Safety Committee.

If the prespecified number of patients discontinues due to maculopapular rash grade 3 during Part A the dose for all the subsequently randomized patients in Part A may be adjusted or study may be stopped. For more information see SRC/DRC charter.

General description of visits:

Visit 1 (enrollment): At visit 1 patients will be asked to sign informed consent. Patients demography, medical and surgical history will be recorded in the electronic Case Report Form (eCRF). To check the patients for eligibility an echocardiography evaluation performed within 1 year and documented in medical records may be used, but if no echocardiography is available a simplified echo screen protocol needs to be performed at visit 1. This echocardiography will focus on Ejection Fraction (EF), LAVI, E/e', Left ventricular mass (LVM) and image analysis will be performed by local echo lab.

Preferably any non-invasive assessments (physical examinations assessments, Blood Pressure (BP) and pulse, weight etc.) will be performed before the echocardiography assessments, if applicable. Blood samples should preferably be taken thereafter, and patient may leave the site after completion of all assessments.

Visit 1 may take place up to 28 days before Visit 2. Subjects may enter a screening period up to 28 days prior to visit 2. If visit 1 is performed more than 14 days prior to visit 2, all assessments except blood and urine sampling should be completed at that visit. Blood and urine samples related to visit 1 must be taken within 14 to 0 days prior to visit 2 to ensure patient eligibility. Visit 1 may occur on the same day as visit 2 if deemed operationally feasible. If so, laboratory sampling for inclusion/exclusion criteria will be analyzed locally but the lab-samples deriving from visit 2 should still be sent to central lab for analysis. If the lab samples analyzed locally meet the inclusion criteria, the patient can be enrolled into the study. In the event that the central lab results are returned and do not meet the inclusion criteria, the patient will not be withdrawn. Other assessments that co-occur at visit 1 and 2 need to be performed only once and recorded in the eCRF according to Completion Guidelines.

For detailed information regarding visits, see SoA

Visit 2 (randomization): Visit 2 should be performed within 28 days (blood and urine samples related to visit 1 must be taken within 14 days to visit 2) from visit 1. Visit 2 could be performed on the same day as visit 1 if deemed operational feasible by site. If the lab samples analyzed locally meet the inclusion criteria, the patient can be enrolled into the study. In the event that the central lab results are returned and do not meet the inclusion criteria, the patient will not be withdrawn.

At visit 2 patients should be asked to arrive to site fasting, see section 5.4.1. Patient should be fasting until CFVR and Endothelial function measurement (EndoPAT™) assessments are performed and laboratory samples are taken.

If patient fulfils all inclusion and none of the exclusion criteria they will be randomized into the study. Preferably any the non-invasive assessments like physical examination, vital signs, KCCQ, ECG, weight, height and body temperature should be performed first, thereafter EndoPAT, and PVW/PWA will follow. Blood sampling is preferably taken before assessment of echocardiography and CFVR and 6MWT. When all assessments are completed the IP will be dispensed and taken at site.

For detailed information regarding visits, see SoA

Visit 3 (Part A): Visit 3 will be performed 10 (±2) days after visit 2. Patients will be asked not to take IP at home on the same day as the visit. At visit 3, treatment will be increased to [redacted] once daily or matching placebo. IP should be administered at site and assessments performed as outlined in SoA.

Visit 3 (Part B): Visit 3 will be performed 10 (±2) days after visit 2. Patients will be asked not to take IP at home on the same day as the visit. At visit 3 treatment may be [redacted] or [redacted] AZD4831 or matching placebo once daily depending on the results from the interim analysis, see section 9.5. IP should be administered at site and assessments performed as outlined in SoA.

Visits 4 and 6 (Part A and Part B): Visit 4 will be performed 20 (±2) days after visit 2, visit 6 will be performed 60 (±4) days after visit 2. At visit 4 and 6 patients should be instructed not to take the IP at home on the same day as the visit. Preferably any non-invasive assessments (physical examination, vital signs, etc.) should be performed before blood sampling. When all assessments are completed the IP will be administered and taken at site. For detailed information regarding visits, see SoA.

Visit 4 and 6 may be performed as home visits if operationally feasible, for assessments performed at home see SoA.

After interim analysis AstraZeneca may decide to make visit 4 and visit 6 in part B to a visit that could optionally be performed as a telephone contact with the patient if judged appropriate by the investigator. In such cases any on-site examinations or laboratory samples will be eliminated and patient will only be asked for any health concerns and/or AEs.

Visit 5 and visit 7 (Part A and Part B): Visit 5 shall be performed 30 (±3) days after visit 2 and visit 7 shall be performed 90 (+2/-7) days after visit 2.

At visits 5 and 7 patients should be asked to arrive to site fasting, see section 5.4.1. Patient should be fasting until CFVR (visit 7) and EndoPAT assessments are performed and laboratory samples are taken. At visit 5 and 7 the patients should be instructed not to take the dose of IP at home before the visit.

For detailed information regarding visits, see SoA

Visit 8 (Part A and Part B): Visit 8 will be performed 120 (±4 days) after visit 2 and will serve as the follow-up visit. Assessments will be performed as outlined in SoA.

4.2 Scientific rationale for study design

Pathophysiology of HFpEF suggests that comorbidities lead to a systemic inflammation, which triggers endothelial and microvascular dysfunction. This results in diastolic stiffness as well as concentric LV remodelling and fibrosis. Presence of diastolic and vascular dysfunction out of proportion to comorbidities and the lack of neurohormonal antagonism benefitting HFpEF patients might suggest a different pathophysiology of HFpEF compared to HFrEF. The microvascular inflammation and dysfunction is the key driver of HFpEF disease progression and leads to excessive mortality and hospitalization. MPO and related biomarkers are significantly elevated in HFpEF patients and studies have shown that MPO genetically and phenotypically is linked to microvascular dysfunction (Mäkelä R et al. 2004).

MPO inhibition is a novel mechanism of action with the intention to become an established treatment option for patients with HFpEF aiming to reduce inflammation and oxidative stress. The rationale for this study is that MPO inhibition through AZD4831 will improve vascular function and this will subsequently lead to increased organ perfusion. Based on evidence discussed above on impact of MPO inhibition on microvascular function, a study treatment of 90 days is considered sufficient to decrease the level of MPO-mediated inflammation and improve myocardial microvascular function, which will be reflected in measurements of inhibition of ex vivo zymosan stimulated MPO specific activity and CFVR. In addition, the study duration is expected to be of sufficient length to permit evaluation of the drug's safety and tolerability profile on top of SoC in HFpEF patients to support further clinical development. To best evaluate the potential effect of AZD4831 the Phase 2a Proof-of-Principle study will be conducted in a randomized, double blind, placebo-controlled design on top of SoC.

Since reproduction toxicology studies have not yet been conducted with AZD4831, females of child-bearing potential are excluded from the study and males are required to abstain from fathering a child or donating sperm for the same reason.

Collection of blood samples for potential future exploratory research into biomarkers related to HFpEF or that may influence drug response to AZD4831, has been included in the study. In

addition, blood samples for potential current and future exploratory genetic research will be collected in patients who have given a separate consent for genetic research.

4.3 Justification for dose

Single doses of up to [redacted] AZD4831 and once daily repeated doses of [redacted] and [redacted] mg for 10 days (14 days for the [redacted] dose) have been well tolerated in healthy patients except for incidences of rash on higher doses (Single Ascending Dose (SAD) study, D6580C00001: [redacted] (1 patient out of 6 treated), [redacted] (1/6) and [redacted] (2/6); MAD: [redacted] (2/6) [redacted] (2/4)). Dosing will start by giving [redacted] once daily for 10 days. The dose will then be increased to [redacted] once daily. The dose of [redacted] is anticipated to give similar exposure in patients as the [redacted] dose in healthy volunteers, since renal clearance is close to total clearance and patients have approximately half the level of eGFR seen in healthy volunteers. At a dose of [redacted] in healthy volunteers, no rash was observed in the MAD study. The procedure of starting with a somewhat lower dose is an attempt to mitigate occurrence of rash by desensitizing the patients to AZD4831. The choice of 10 days of dosing with the lower dose is because all incidences of rash observed in the SAD and MAD (D6580C00001) studies appeared around day 7-9 after the first dose.

The [redacted] dose in healthy volunteers resulted in around 50% inhibition of ex vivo zymosan stimulated MPO specific activity (MPO activity divided by MPO protein mass) at steady state when normalizing for the maximum detectable MPO inhibition (subtraction of the ex vivo zymosan stimulated MPO specific activity obtained in a pre-dose blood sample in presence of excess AZD4831). Published data support a 50% inhibition of MPO activity to result in clinically relevant improvement in vascular function. Releasing MPO from the vessel wall using heparin resulted in improvement in Flow Mediated Dilatation (FMD) (Baldus et al 2006). Furthermore, patients with low MPO activity levels had no deterioration in FMD following nicotine challenge, as compared to patients with normal MPO activity levels where nicotine challenge resulted in a deterioration in FMD (Rudolph et al 2012).

At the interim analysis target engagement, in form of level of MPO inhibition as measured by normalised *ex vivo* zymosan stimulated specific MPO activity, will be evaluated. The intention is to use the [redacted] dose throughout the study (after a starting dose of [redacted] for the first 10 days). However, pending outcome of the interim analysis, there is a possibility to either increase the dose to [redacted] for the following patients in the study should there be too low target engagement and minimal rash, or to lower the dose to [redacted] should there be good target engagement but too high incidence of rash. For both the [redacted] and the [redacted] alternatives, dosing will start by 10 days with [redacted] once daily followed by either [redacted] or [redacted] once daily.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

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

Each patient should meet all the inclusion criteria and none of the exclusion criteria to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to section 5.4.

In this protocol, “enrolled” patients are defined as those who sign informed consent. “Randomized” patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this CSP

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses

The ICF process is described in Appendix A 3

Age

3. Patient must be 45 to 85 years of age inclusive, at the time of signing the informed consent form

Type of patient and disease characteristics

4. Signs and symptoms of HF in judgement of Investigator AND

   a. Stable NYHA II-IV and

   b. EF ≥ 40 % and

   c. Elevated NT-proBNP or BNP in the last 1 year defined as:

   - Measured as out-patient: NT-proBNP ≥125 ng/L or BNP≥35 ng/L with sinus rhythm, NT-proBNP ≥750 ng/L or BNP ≥200 ng/L with atrial fibrillation (AF),

     or

   - Measured when hospitalized acutely: NT-proBNP ≥500 (ng/L) or BNP ≥125 ng/L with sinus rhythm, NT-proBNP ≥1250 (ng/L) or BNP ≥350 ng/L with AF

   d. And <u>at least one</u> of the following:

   - Hospitalization with HF as primary cause in last 12 months
   - Structural heart disease on echo according to ESC guidelines i.e. either enlarged Left atrial volume index (LAVI > 34 ml/m2) or increased LVM (LVM index > 95 g/m2 in women and > 115 g/m2 in men)
   - Pulmonary capillary wedge pressure (PCWP) at rest >15 mmHg or >25 mmHg at exercise
   - Spectral tissue Doppler echocardiography - E/e' ratio ≥13 at rest

Weight

5. Body Mass Index (BMI) range 18- 40kg/m^2

Sex

6. Male or female of nonchildbearing potential

Reproduction

7. Female patients must be 1 year post-menopausal or surgically sterile

8. Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of AZD4831/matching placebo to prevent pregnancy in a partner. Male patients must not donate or bank sperm during this same time period

Genetic sampling

9. For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described above and provide informed consent for the genetic sampling and analysis

5.2 Exclusion criteria

Medical conditions

1. Creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR <30 ml/min/1.73m2 or dialysis

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

3. Any ongoing skin disorder, history of or ongoing clinically significant allergy/hypersensitivity

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4. Current decompensated HF

5. Primary cardiomyopathy (e.g. constrictive, restrictive, infiltrative, toxic, hypertrophic, congenital or any primary cardiomyopathy) in judgment of investigator

6. Current hemodynamically significant valve disease in opinion of investigator

7. Any condition with indication for cardiac surgery or catheter intervention

8. EF ever documented < 40%

9. Any event (e.g. acute myocardial infarction) that may have reduced EF, that occurred after the echocardiogram used for inclusion, unless repeat echocardiogram confirms EF ≥ 40%

10. Tachycardia > 110 bpm

11. Any current life-threatening dysrhythmia

12. Probable alternative primary reason for patient's symptoms in judgment of investigator, including but not limited to:

    a. Isolated pulmonary arterial hypertension or right ventricular (RV) failure; in the absence of left-sided HF

    b. Anaemia: Hb <100 mg/L (10g/dL)

c. Severe chronic obstructive pulmonary disease (COPD) or lung disease (chronic O2, nebulizer or oral steroid therapy)

13. Cardiac surgery, acute coronary syndrome (ACS), or non-elective percutaneous coronary intervention (PCI) < 3 months

14. Known or clinically judged significant macrovascular coronary artery disease (CAD) that has not been revascularized

15. Any non-elective hospitalization < 2weeks

16. Current significant major or unstable respiratory disease, haematological disease, hepatic disease, renal disease, gastrointestinal (GI) disease, or other major treatment required disease as judged by the investigator.

17. Stroke, transient ischemic attack, carotid surgery or angioplasty within 3 months

18. Heart transplantation or left ventricular assist device ever

19. Patients with hypertension (unstable or untreated) or symptomatic hypotension (that in the opinion of the investigator requires treatment)

20. Patients with uncontrolled or clinically significant thyroid disease as judged by the investigator

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

22. Alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥2 x upper limit of normal (ULN). Resampling will not be allowed during the same screening period if detected abnormal values do not have reasonable explanation and are not expected to return to normal level within few days.

23. Known positive HIV, hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody, at screening

24. Plasma donation within 1 month of enrollment or any blood donation/blood loss >500 mL during the 3 months prior to enrollment.

25. For CFVR:

    a. Known allergy to adenosine

    b. Known elevated intracranial pressure

c. AV block ≥ second degree and/or sick sinus syndrome in patient without pacemaker

d. Heart rate < 50 bpm

e. Systolic blood pressure < 90 mmHg

f. Asthma or COPD with strong reactive component in judgment of investigator

g. Treatment with dipyridamole, theophylline or fluvoxamine within 24 h or caffeine containing beverages within 12 h

26. Any circumstances in which in the investigator's opinion makes it undesirable for the patient to participate in the trial.

27. Known history of drug or alcohol abuse within 1 year of screening

28. History of QT prolongation associated with other medications that required discontinuation of that medication.

29. Congenital long QT syndrome.

30. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment, uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.

Prior/concomitant therapy

31. Any concomitant medications known to be associated with Torsades de Pointes or potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors e.g. itraconazole, rifampicin, clarithromycin

Prior/concurrent clinical study experience

32. Participation in another clinical study with an investigational product administered in the last 3 months (or 5 half-lives).

Other exclusions

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

34. Any condition, e.g. ongoing drug abuse, which may interfere with participation or safety of investigations or interferes with participation, in the opinion of the investigator

35. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

36. Previous randomization in the present study

5.3 Prevalence of Atrial Fibrillation in study population

Prevalence of AF in the study population should not exceed 50%.

Interactive voice/web response system (IxRS) will be preset accordingly.
Whenever possible, it is recommended to keep the difference in prevalence HFmrEF and HFpEF between the groups on a reasonably comparable level.

5.4 Lifestyle restrictions

5.4.1 Meals and dietary restrictions

Patient should arrive to the clinic after fasting overnight (no food or liquid [except for water] intake permitted 12 hours before the visit) for Visits 2, 5, 7 for sampling of safety laboratory samples, CFVR and EndoPAT measurements.

In case patient has not been fasted for 12 hours prior the visit it should be rescheduled.

5.4.2 Caffeine, alcohol, and tobacco

Prior to Visits 2, 5 and 7 avoid intake of coffee or other caffeine containing beverages 12 hours before and until after completion of the study specific clinical assessments (CFVR, Echo).

Abstain from tobacco/nicotine for at least 120 minutes prior to CFVR measurements, or whenever study procedures demand it. Nicotine substitutes will be offered at the discretion of the Investigator

Abstain from excessive intake of alcohol for 48 hours preceding all the clinical visits.

Abstain from drugs of abuse during the entire study.

5.4.3 Activity

In conjunction with visit 2, 5 and 7 patients should avoid excessive physical activity 24h prior visit.

5.4.4 Reproductive restrictions

There is no information about effects that AZD4831 could have on the development of the foetus in humans. Pre-clinical studies have shown that AZD4831 is not genotoxic, however formal pre-clinical reproductive toxicology studies have not yet been completed. Women of child-bearing potential will not be included in this study (for definition see inclusion criteria). In addition, it is important that women of childbearing potential, who are the partners of male patients, do not become pregnant during the study and for a total period of 3 months after the male study patient has received his last dose of IP.

All male patients should avoid fathering a child by either true abstinence or use together with their female partner/spouse a highly effective method of contraception (see definition below), starting from the time of IP administration until 3 months after the last dose of IP. For male patients whose partner is pregnant, the man should use a condom for the duration of the study and for 1 week afterwards.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion of female partner
- Male vasectomy
- True sexual abstinence

True abstinence refers to: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Sperm Donation

Male patients should not donate sperm for the duration of the study and for at least 3 months after his last dose of IP.

Pregnancy

Male patients will be instructed that if their partner becomes pregnant during the study this should be reported to the Investigator. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient's partner is subsequently found to be pregnant after the study patient is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

5.5 Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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 do not meet the criteria for participation in this study (screen failure) may be rescreened one time after 1 month if they fulfil the inclusion/exclusion criteria then. The patient should sign a new informed consent if rescreened.

These patients should have the reason for study withdrawal recorded in the eCRF.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the CSP. Study treatment in this study refers to AZD4831 or matching placebo.

6.1 Treatments administered

6.1.1 Investigational products

Table 3 Study Treatments

	AZD4831	Placebo	AZD4831	Placebo	AZD4831	Placebo
Study treatment name:	AZD4831 [redacted]	Matching placebo [redacted]	AZD4831 [redacted]	Matching placebo [redacted]	AZD4831 [redacted]	Matching placebo [redacted]
Dosage formulation:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosage formulation:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Dosing instructions:	Once daily	Once daily	Once daily	Once daily	Once daily	Once daily
Packaging and labelling	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements
Provider	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca

6.2 Preparation/handling/storage/accountability

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

Only patients randomized in the study may receive IP and only authorised site staff may supply or administer IP. All IP 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.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The investigator will retain the returned IP until the AZ representative or delegate collects it, along with any IP not dispensed. The AZ representative or delegate is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before IP is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused IP.

6.3 Measures to minimise bias: randomization and blinding

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

All patients will be centrally assigned to randomized IP using an interactive voice/web response system (IxRS). Randomization to IP will be performed in balanced blocks to ensure approximate balance between the treatment groups (2:1). The randomization codes will be computer generated and loaded into the IxRS database. Before the study is initiated, the telephone number and call-in directions for the IxRS and/or the log-in information and directions for the IxRS will be provided to each site.

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

The IxRS will provide to the Investigator or pharmacist the kit identification number to be allocated to the patient at the dispensing visit. At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient. Routines for this will be described in the IxRS user manual that will be provided to each centre.

The IxRS will be programmed with blind-breaking instructions. The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca within 24 hours after breaking the blind, without revealing the treatment given to the patient to the AstraZeneca staff. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

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

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

6.3.1 Stratification

The randomisation will be stratified by Atrial Fibrillation (Yes vs No).

6.4 Treatment compliance

The administration of IP should be recorded in the appropriate sections of the eCRF. Any change from the dosing schedule should be recorded in the eCRF.

Patients will be asked to bring the IP bottle to the clinic at all site visits (except at visit 4 and visit 6) to check IP compliance. At each visit, any patient found to be non-compliant will be counselled on the importance of taking their IP as prescribed. The investigator or delegate will enter the number of returned tablets in the eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

Diary Cards will be given to the patients at the randomization visit and the patients will be asked to fill in the dose intake information for each dose (date and time) at home. The diary cards will be checked by study site personnel at the study visits and data transferred to the eCRF.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment 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

Concomitant medication not allowed within 24 h prior to visits including CFVR examinations are listed in the exclusion criteria (last bullet), Section 5.2.

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Table 4 Prohibited medications

Prohibited medication/class of drug:
- Cyclosporin or Tacrolimus
- Potent Inhibitors CYP3A4
1) protease inhibitors: ritonavir, indinavir, nelfinavir, saquinavir, atazanavir, darunavir, lopinavir, tipranavir 2) macrolide antibiotics: clarithromycin, telithromycin 3) chloramphenicol (antibiotic) 4) azole antifungals: ketoconazole, itraconazole, posaconazole, voriconazole 5) nefazodone (antidepressant) 6) cobicistat
- Potent Inducers CYP3A4
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

Table 4 is not a complete list of potent CYP3A4 inhibitors/inducers. Please refer to concomitant medications SmPCs for further information and clarification

6.5.1 Background medication

The patients should be on stable background treatment and have no intended dose change of the background therapy within the period of the study treatment.

6.5.2 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF. If this is one of the prohibited medications listed above, the study drug must be discontinued, and the patient withdrawn from the study.

6.5.3 Rescue medication

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

6.6 Dose modification - Not Applicable

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

At each visit patients will be instructed to contact the investigator immediately, if rash has developed. If maculopapular rash grade 1 and/or grade 2 has developed, the decision to continue treatment will be made by investigator in discussion with patient and AstraZeneca medical staff. If maculopapular rash grade 3 has developed, patient must be discontinued from IP and AstraZeneca medical staff should be informed.

- Grade 1: Macules/papules covering **< 10% Body Surface Area** with or without symptoms (e.g., pruritus, burning, tightness).
- Grade 2: Macules/papules covering **10 - 30% Body Surface Area**, with or without symptoms (e.g., pruritus, burning, tightness); limiting Instrumental **Activities of Daily Living (**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 **Activities of Daily Living (**refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

For further information and rash evaluation guidance see Appendix B9.

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the CSP

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

See section 7.1.3 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

Temporary discontinuation of study medication is NOT permitted in this study.

7.1.2 Rechallenge

Rechallenge of study medication is NOT permitted in this study.

7.1.3 Procedures for discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if IP is stopped. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. The date of last intake of IP should be documented in the eCRF. All IP should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing IP should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of IP for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the CSP. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. Preferably the patient will be seen for an end-of treatment visit (visit 7). This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient or next of kin by e.g. repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.

- Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

- AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

7.3 Withdrawal from the study

A patient may withdraw from the study (e.g., withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

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

If the patient 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 patient withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up patients as medically indicated.

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All IP should be returned by the patient.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of the treatment must be documented.

7.4 Study termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The study may be terminated if, in the judgement of the sponsor, trial patients are placed at undue risk.
- Patient enrollment is unsatisfactory

- Non-compliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate development

Premature termination of the study must be mutually agreed upon by the PI and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded in the eCRF. A Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF copy of the completed eCase Report Forms, and it will be archived at the study site.

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

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 patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., 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 patient over the duration of the study, including any extra assessments that may be required, will not exceed 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Target engagement assessment

Target engagement will be assessed through measuring *ex vivo* zymosan stimulated MPO specific activity (MPO activity divided by MPO protein mass), normalised.

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual at timepoints described in the SoA

8.1.2 Clinical outcome assessments

8.1.2.1 Echocardiography

Comprehensive echocardiographic examination will be performed with patients in the left recumbent position at rest. Standard clinical cardiac transducers will be used for B-mode, colour Doppler, and tissue Doppler imaging. CINE-loops[1] of the parasternal long- and short-axis views, apical 4-, 2-, and 3-chamber views, and subcostal views will be obtained and stored for off-line analysis of cardiac structure and function, as detailed in the Manual of Procedures (MoP) for Echocardiography (detailed echocardiography protocol) 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 diastolic function and non-invasive hemodynamic measurements, as detailed in MoP.

If echocardiography data from examination within 1 year is available in medical records that may be used for incl./excl. criteria. If not available a simplified echo screen protocol needs to be performed at visit 1. For screening echocardiography focus will be on EF, LAVI, E/e', LVM and image analysis will be performed by local echo lab.

8.1.2.2 Transthoracic Doppler echocardiography (TDE) with coronary flow velocity reserve (CFVR) measurement

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

8.1.2.3 Carotid-femoral Pulse Wave Velocity (cfPWV) and brachial Pulse Wave Analysis (bPWA)

Carotid-femoral pulse wave velocity (cfPWV) is measured in a single step with a simultaneous measurement by femoral cuff and carotid placed tonometer. Brachial pulse wave analysis (bPWA) is conducted with a brachial cuff recording. For details see MoP.

[1] A CINE-loop is a period of images, stored digitally as a sequence of individual frames. CINE-loops recorded at high frame rates may contain more frames than were displayed during the examination

8.1.2.4 Endothelial function measurement - EndoPAT™

The endothelial function measurement by peripheral arterial tonometry (EndoPAT™) will be conducted based on instructions provided by the EndoPAT™ device distributor (Itamar Medical Ltd., Caesarea, Israel).

For detailed description of the EndoPAT™ measurement procedures please refer to MoP.

8.1.2.5 6 Minute Walk Test (6MWT)

The Six-Minute Walk Test will be conducted based on the American Thoracic Society (ATS) Guidelines. For detailed description of the 6MWT procedures please refer to MoP.

8.1.2.6 Laboratory assessments

Blood samples for the following assessments will be drawn:

Table 5 Laboratory assessments

Efficacy laboratory assessments	
TE Biomarker	*Visit 2, Visit 3, Visit 5 and Visit 7*
BNP or NT-proBNP	*BNP or NT-proBNP at visit 1* *NT-proBNP at Visit 2, Visit 5 and Visit 7*
Lipid status assessments	
Cholesterol	*Visit 2 and Visit 7*
LDL	*Visit 2, Visit 5 and Visit 7*
HDL	*Visit 2, Visit 5 and Visit 7*
TG (triglycerides)	*Visit 2 and Visit 7*
ApoA1	*Visit 2 and Visit 7*
ApoB	*Visit 2 and Visit 7*
Other laboratory assessments	
Cystatin-C	*Visit 2, Visit 5 and Visit 7*
hs-TNT	*Visit 2, Visit 5 and Visit 7*
HbA1c	*Visit 2, Visit 5 and Visit 7*
Blood urea nitrogen	*Visit 2, Visit 5 and Visit 7*
Insulin	*Visit 2, Visit 5 and Visit 7*
Exploratory Biomarkers (see section 8.8)	*Visit 2, Visit 4, Visit 5, Visit 7, Visit 6 and Visit 8*
Endogenous MPO (see section 8.8)	*Visit 2, Visit 5 and Visit 7*

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

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 6 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the tables, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date and time of collection will be recorded on the appropriate eCRF.

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

Table 6 Safety Laboratory Assessments

Haematology/Haemostasis (whole blood)	
B-Haemoglobin (Hb)	*At each visit*
B-Leukocyte count	*At each visit*
B-Leukocyte differential count (absolute count)	*At each visit*
B-Platelet count	*At each visit*
Clinical Chemistry (serum or plasma)	
S-Creatinine	*At each visit*
S-Bilirubin, total	*Visits 1, 2, 3, 5, 7 and 8*
S-Alkaline phosphatise (ALP)	*Visit 1, 2, 3, 5, 7 and 8*
S-Aspartate transaminase (AST)	*Visit 1, 2, 3, 5, 7 and 8*
S-Alanine transaminase (ALT)	*Visit 1, 2, 3, 5, 7 and 8*
TSH	*Visit 1, 2, 5, 7 and 8*
T4	*Visit 1, 2, 5, 7 and 8*
T3	*Visit 1, 2, 5, 7 and 8*
LH	*Females only, only visit 1*
FSH	*Females only, only visit 1*
S-Albumin	*Visit 1, 2, 3, 5, 7 and 8*
S-Potassium	*At each visit*
S-Calcium, total	*Visit 1, 2, 3, 5, 7 and 8*
S-Sodium	*At each visit*
S-Creatine kinase (CK)	*Visit 1, 2, 3, 5, 7 and 8*
Glucose (fasting)	*Only Visit 2, 5 and 7*
hs-CRP	*At each visit*
Urinalysis (dipstick)	
U-Hb/Erythrocytes/Blood	*Visit 1, 2, 3, 5, 7 and 8*
U-Protein/Albumin	*Visit 1, 2, 3, 5, 7 and 8*
U-Glucose	*Visit 1, 2, 3, 5, 7 and 8*
Uric Acid	*Visit 1, 2, 3, 5, 7 and 8*

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

Table 7 Other Clinical Safety Panels

Panel Name	Markers
Serology (Screening only)	Human immunodeficiency virus (HIV) I and II
	Hepatitis B surface antigen (HBsAg)
	Hepatitis C virus antibody

8.2.2 Physical examinations

A complete physical examination will be performed at enrolment (visit 1), visit 4 and at Follow-up (visit 8) and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities) and neurological systems. On the other occasions a brief physical examination (general appearance, skin, abdomen and musculoskeletal, cardiovascular and respiratory systems) will be conducted.

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7

8.2.3 Skin Rash

Skin rash (if any) will be documented as follows: start date, severity, body surface area, anatomical site, symptoms, signs, effect on patient, medication administered. Photos (overview and detailed) should be taken. All skin rash reactions should be recorded as AEs, with the evaluation of severity as Grade 1, 2 or 3. Corresponding rash related eCRF page should be filled out as soon as possible.

Please refer to Appendix B9 for further guidance in rash assessment and reporting.

Upon PI discretion, clinical dermatologist can be asked for consultation, and providing patient with the treatment of skin rash, according to clinical management standards.

8.2.4 Vital signs

Blood pressure and pulse measurements will be assessed prior to collection of laboratory tests with patient in resting semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded in the eCRF.

Weight, height and body temperature will be assessed as outlined in SoA.

8.2.5 Electrocardiograms

Single 12-lead ECG will be obtained after the patient has been resting in a supine position for at least 10 minutes, at the visits outlined in the SoA. 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.

8.3 Collection of adverse events

The Principal Investigator 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.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 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.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs/non- serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient'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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- 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

8.3.5 Causality collection

The Investigator will assess causal relationship between IP and each Adverse Event, 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 will 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 CSP.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit?'*, 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.

8.3.7 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (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 or are the reason for discontinuation of treatment with the investigational product.

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 (e.g., 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.

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN 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.

8.4 Safety reporting and medical management

8.4.1 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, then Investigators or other site personnel should inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by fax (+46 31 776 37 34) or E-mail (AEMailboxWBDCTCS@astrazeneca.com).

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant eCRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

Women of child-bearing potential are not permitted to participate in this study. Male study patients with female partners of child-bearing potential must adhere to the reproductive restrictions provided in Section 5.4.4.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for if the female partner of a male study participant discovers she is pregnant before the study patient has received any study drug.

If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy.

8.4.2.1 Maternal exposure

Women of childbearing potential are not permitted to participate in this study (see inclusion criteria for definition of women not of child-bearing potential). Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

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 abnormalities/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 abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) 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 PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

See section 5.4.4

8.4.2.3 Overdose

For this study, any dose of AZD4831 greater than specified in the CSP will be considered an overdose. There is no recommended specific treatment for 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 AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

- For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.4.1. For other overdoses, reporting must occur within 30 days.

8.4.3 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca 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 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B8.

8.5 Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement for plasma concentrations of AZD4831 as specified in the SoA. Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. Diary Cards will be given to the patients at the randomization visit and the patients will be asked to fill in the dose intake information (date and time) at home.

If data permits, a population PK model will be developed, possibly with support of PK data from previous studies with AZD4831, using non-linear mixed effect regression analysis in NONMEM. All PK, and PK/PD, modelling work will be described in a separate data analysis plan. Moreover, the results of such modelling will be provided in a separate population PK, or PK/PD, report (as an appendix to the CSR or as a stand-alone 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.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration will be analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report. PK concentrations may be assessed during the study for evaluation of the exposure levels.

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

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

Approximately 6mL blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Exploratory Biomarkers

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

Samples will be collected, labelled, stored and shipped according to the details outlined in the laboratory manual.

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or

publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Patient Reported Outcome Questionnaires

8.9.1 The Kansas City Cardiomyopathy Questionnaire (KCCQ)

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

KCCQ will be answered by patients on paper at visits as outlined in SoA, Table 1 and recorded in the eCRF by site staff.

8.10 Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Statistical hypotheses are described in section 9.4 and further details will be provided in the Statistical Analysis Plan (SAP).

9.2 Sample size determination

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

In addition, to get information about incidence rate of Generalised Maculopapular Rash Grade 3 in the AZD4831 arm a randomisation allocation ratio of 2:1 (active versus placebo) will be used. With approximately 96 randomized patients, this will give at most 64 patients on active drug for rash evaluation and about 53 patients on AZD4831 versus 27 patients on placebo for

evaluation of the first primary endpoint and the first secondary endpoint. It has been deemed that about 64 patients provide sufficient information about the incidence rate of rash when treated with AZD4831.

A relative change in TE biomarker to end of treatment comparing AZD4831 to placebo is assumed to be log-normal distributed with a CV of 60% (based on data from the MAD study). An expected reduction of 15% from baseline to end of treatment in TE biomarker in placebo, and an expected reduction of 50% from baseline to end of treatment in TE biomarker in AZD4831 are assumed (based on data from the MAD study, Baldus et al 2006). A foldchange of at least 1.7 in TE biomarker comparing AZD4831 to placebo will give more than 95% power for a two-sided test on a 5% significant level with 53 patients on AZD4831 versus 27 patients on placebo, accounting for patient drop out. If the dose level is adjusted after the interim analysis the power will still be at least 90% for testing the primary endpoint hypothesis with the assumption of 25 patients on AZD4831 and 25 patients on placebo.

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

9.3 Populations for analyses

9.3.1 Full analysis set

All patients who have been randomized to investigational product (IP) will be included in the full analysis set irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomized IP irrespective of whether or not they have prematurely discontinued. Patients who withdraw consent to participate in the study are included up to the date of their study termination.

9.3.2 Safety analysis set

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

9.3.3 PK analysis set

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

9.4 Statistical analyses

This section provides a summary of the planned statistical analyses. Further details will be provided in a SAP. All study personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified. The only exception are study independent personnel who are involved in the interim analyses.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

All efficacy and safety variables will be summarised by treatment groups using descriptive statistics (n, mean, geometric mean, standard deviation [SD], median, minimum, maximum, and coefficient of variation [CV] where applicable for continuous data and absolute and relative frequencies for categorical data). Data will be summarised for baseline, endpoint and by visit (if applicable). P-values will be unadjusted and tests will be two-sided. For the primary efficacy variable TE biomarker a two-sided test will be used and first secondary efficacy variable CFVR a one-sided test will be used. A closed test procedure will be applied to control the overall type 1-error rate due to multiplicity for the primary endpoint and the first secondary endpoint. All tests, unless otherwise stated, will be performed between the AZD4831 group versus placebo. The analyses will be done separately for each dose level if the dose has been changed at the interim analysis.

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

Descriptive statistics will be presented to assess the distribution of the baseline variables across treatment groups.

The analysis and presentation of efficacy variables, exploratory variables and exploratory biomarkers will be based on patients in the full analysis set. All efficacy variables will be summarised descriptively displaying parameter values at visits where they were measured.

The analysis and presentation of safety variables will be based on patients in the safety analysis set.

Baseline measurement is defined as last measurement obtained before or at the randomization visit if nothing else is specified.

Change from baseline is defined as change from baseline to end of treatment if nothing else is specified.

9.4.1 Efficacy analyses

The primary efficacy variable TE biomarker and first secondary efficacy variable CFVR are measured as percent change from baseline to end of treatment comparing AZD4831 to placebo.

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

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

Change from baseline for the primary and first secondary efficacy variables will be analysed using an ANCOVA model. The result will be presented as point estimate with 95% confidence intervals together with p-values.

All other secondary variables measuring change from baseline will be analysed using an ANCOVA model. If the distribution of the variable of interest can be better approximated by a log-normal distribution than with a normal distribution, a logarithmic transformation of the variable of interest will be done.

9.4.2 Safety analyses

AEs will be summarised by treatment group by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT). All AEs will be listed and assigned to treatment period as:

- Baseline period: The time before first administration of IP.
- On treatment: The time from first administration of IP until 14 days after last dose of IP.
- Off treatment: More than 14 days after last dose of IP.

AEs will be assigned to the period where they start.

Clinical laboratory, physical examination and vital signs measurements will be summarized by treatment group.

Laboratory data for haematology and clinical chemistry will be summarized by treatment group. The frequency of changes with respect to normal ranges between baseline and end of treatment will be tabulated. Shifts from normal to abnormal between baseline and end of treatment time point will be evaluated for urinalysis. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarised by treatment

group. Categorical outliers may be presented by numbers but need to be considered in context of inclusion/exclusion criteria. Vital signs variables will be summarised by treatment group.

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

The patients who discontinue due to generalised maculopapular rash grade 3 will be presented as point estimate of incidence rate by treatment group together with 95% confidence interval.

Other safety variables will be summarised as appropriate. Further details will be provided in the SAP.

9.4.3 Exploratory analysis

All exploratory variables and exploratory biomarkers measuring change from baseline will be analysed using an ANCOVA model.

Patients with elevated MPO-pathway biomarkers will be identified and for all secondary variables and exploratory variables change from baseline will be analysed using an ANCOVA model.

9.4.4 Other analyses

If data permits, a population PK model will be developed, possibly with the support of PK data from earlier AZD4831 studies, using nonlinear mixed effects regression analysis in NONMEM. Furthermore, if data allows, the population PK model may be coupled with separate PD models for spike normalised *ex vivo* zymosan stimulated specific MPO activity and for CFVR.

All PK and PK/PD modelling will be described in a separate data analysis plan. Moreover, the results of any such modelling will be provided in a separate population PK/PD report (as an appendix to the CSR or as a stand-alone report).

9.5 Interim analyses

An interim analysis will be performed after 37 patients, 25 on AZD4831 and 12 on placebo, have been treated for approximately 30 days in Part A. The interim analysis will be used for selecting dose for Part B or to stop the study. The decision on dose adjustment or whether to stop the study will be based on the level of TE biomarker and the number of patients discontinued due to generalised maculopapular rash grade 3. Only patients treated with AZD4831 will be included in the analysis. The possible outcomes of the interim analysis are continuing with [redacted] decrease the dose to [redacted], increase the dose to [redacted] or stop the study. The interim analysis will be performed by study independent personnel. The Interim Analysis Plan will describe the planned interim analyses in detail.

9.6 Safety Review Committee

A blinded Safety Review Committee (SRC) consisting of internal AstraZeneca (AZ) expertise will review safety data related to rash on an ongoing basis throughout the study and give input and recommendations to a Data Review Committee (DRC). For more information refer to SRC/DRC charter.

9.7 Data Review Committee

The number of patients who discontinue the study due to generalised maculopapular rash CTCAE grade 3 or higher will be continuously monitored by a Data Review Committee (DRC) and the study will be stopped if at any time the proportion of discontinued patients on AZD4831 is above a prespecified level. The DRC consists of internal AZ expertise.

The statistical monitoring will be described in the SRC/DRC charter that must be finalised before first patient in.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONSREGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the CSP 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 Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The CSP, 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- 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), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

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 patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative 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 patient was enrolled in the study and the date *and time* the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients 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 patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after 1 month if they fulfil the inclusion/exclusion criteria then. The patient should sign a new informed consent if rescreened.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the further genetic and exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give separate agreements to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research. The response to these separate agreements will be recorded in the eCRF.

A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient 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 must also be explained to the patient.

The patient 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

SRC and DRC is described in separate SRC/DRC charter.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF 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 physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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 15 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 patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF 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.

Definitions of what constitutes source data can be found in source data verification plan.

A 9 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 event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient 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 (e.g. 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 treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

B 3 Life threatening

'Life-threatening' means that the patient 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 patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 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 jeopardize the patient 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 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 7 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 patient 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 recognized 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 limited or insufficient information in the case, it is likely that 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 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug 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 recognize that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. 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 e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - 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) e.g. 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.

B 9 Guide to skin rash severity assessment

This Appendix describes the process to be followed to appropriately identify, assess and report cases of skin rash. All skin rash reactions should be recorded and reported as AEs, with the evaluation of severity as Grade 1, 2 or 3.

If maculopapular rash Grade 1 or Grade 2 has developed, the decision to continue treatment will be done by investigator in discussion with patient and AstraZeneca medical staff.
If maculopapular rash Grade 3 has developed, patient must be discontinued from IP, and AstraZeneca medical staff should be informed. Investigator should make quality photo(s) of patient's skin affected with rash, that will allow the evaluation of rash according to the guidance given in this section. These photo(s) should be also provided to the Astra Zeneca Safety Committee.

The Common Terminology Criteria for AEs is a descriptive terminology used for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

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; hospitalization or prolongation of hospitalization 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.

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

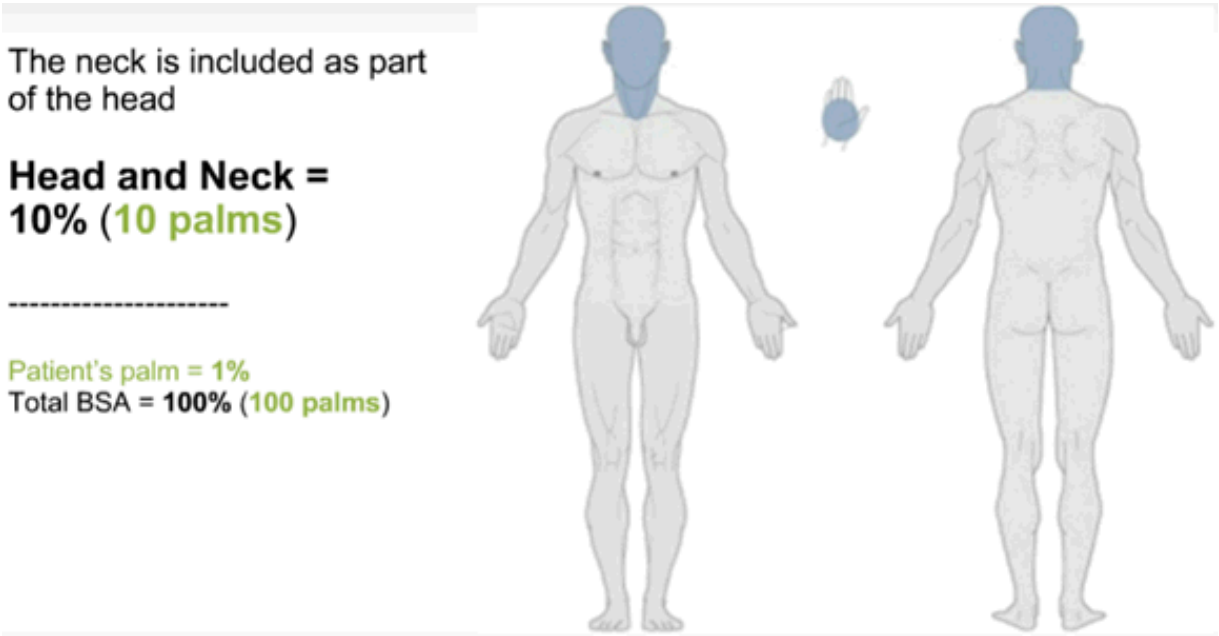
Maculo-Papular Rash	
Definition: *A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.*	
Grade 1	Macules/papules covering **< 10% Body Surface Area** with or without symptoms (e.g., pruritus, burning, tightness)
Grade 2	Macules/papules covering **10 - 30% Body Surface Area**, with or without symptoms (e.g., 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. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Publish Date November 27, 2017.

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

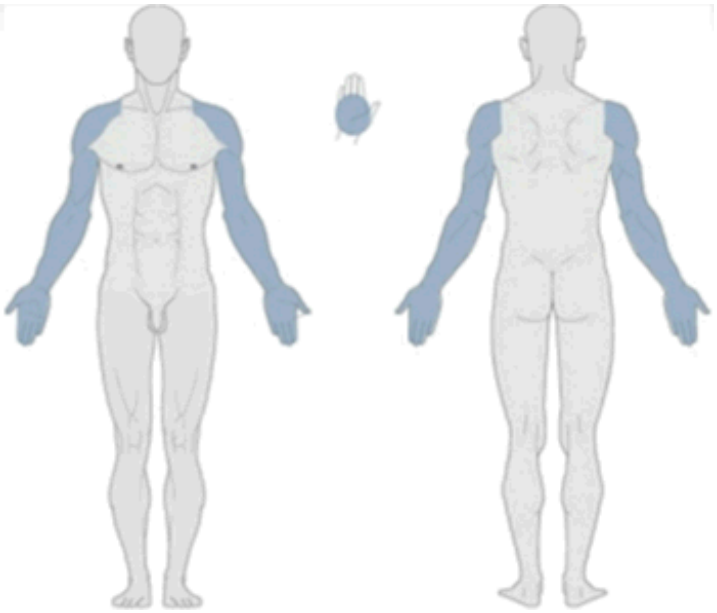
Area	Number of palms	Percent area
Whole body	100	100%
Head and Neck	10	10%
Upper extremities	20	20%
Trunk	30	30%
Lower extremities	40	40%

The patient's palm is defined as "1", representing 1% of total Body Surface Area (BSA). Total BSA = 100% (100 palms).



Upper extremities
= 20% (20 palms)

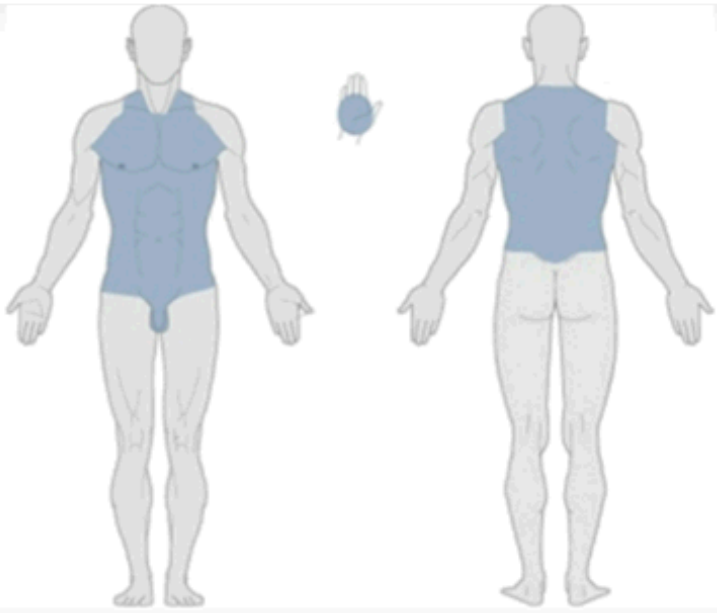
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The axillae and genitals are included with the trunk

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

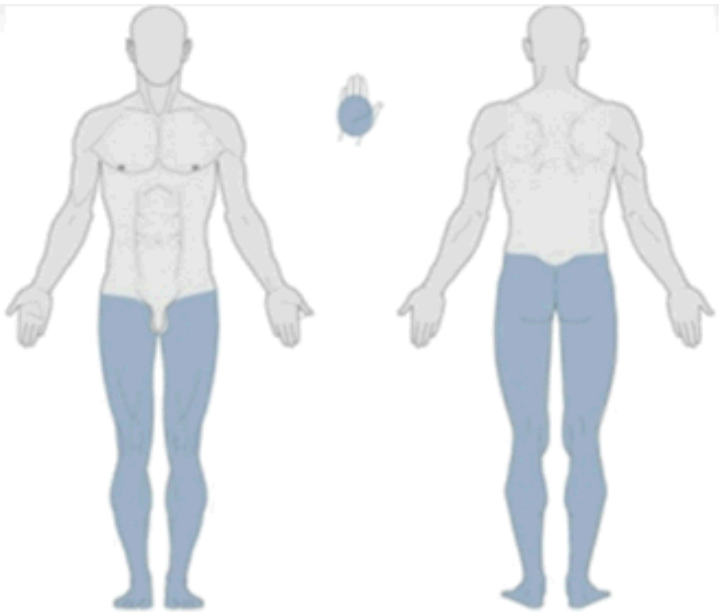
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



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 of biological samples

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 patients while in storage at the centre until shipment or disposal (where appropriate).

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 documentation of receipt of arrival.

AstraZeneca 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 and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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:

- are to be packed and shipped in accordance with IATA Instruction 602.

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, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

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. 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.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on AZD4831 or other AstraZeneca Study treatments of this class or for this indication continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the genetic 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:
Patients 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 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the patients at Visit 2 randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The process adopted for the single coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient 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 blood 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 AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca 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 patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection
AstraZeneca will not provide individual genotype results to patients, 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 patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management
Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations 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 patient 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.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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 Potential Hy's Law (PHL) cases and Hy's Law (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 subject 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 AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAE) and Adverse Events (AE) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. 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 subject who meets any of the following identification criteria in isolation or in combination:

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

When a subject 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 AstraZeneca 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 AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF 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 subject meets PHL criteria (see Section 2 within this Appendix 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 patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient 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 subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca 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 subjects 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 subject's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available

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 AstraZeneca 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.

Whether 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 CRF

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs 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 AstraZeneca 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 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.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix F Medical device incidents: definition and procedures for recording, evaluating, follow-up, and reporting – Not Applicable

Appendix G The Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

Study ID# ☐☐☐☐☐

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.

Please place an ☒ 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
☐	☐	☐	☐	☐	☐

Study ID# ☐☐☐☐☐

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 per 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
☐	☐	☐	☐	☐	☐	☐

Study ID# ☐☐☐☐

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
☐	☐	☐	☐	☐

Study ID# ☐☐☐☐

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 ☒ 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	☐	☐	☐	☐	☐	☐

Appendix H Abbreviations

Abbreviation or special term	Explanation
6MWT	6 Minutes Walking Test
AE	adverse event
ACS	Acute Coronary Syndrome
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AV	Atrioventricular
AZ	AstraZeneca
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats/minute
CAD	Coronary Artery Disease
CFVR	Coronary Flow Velocity Reserve
cGMP	Cyclic Guanosine Monophosphate
CKD-EPI	Creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CSP	Clinical study protocol
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP3A4	Cytochrome P450 SA4
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular filtration rate
EndoPAT	A method for Endothelial function measurement
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
FMD	Flow Mediated Dilatation
GCP	Good Clinical Practice
GI	Gastrointestinal
GLS	Global longitudinal strain

Abbreviation or special term	Explanation
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
HL	Hy´s Law
ICH	International Conference on Harmonisation
IUD	Intrauterine device
IUS	Intruuterine hormone-releasing system
IP	Investigational Product
IRB/IEC	Institutional review board (IRB) and independent ethics committee (IEC)
IxRS	Intractive voice/web response system
KCCQ	The Kansas City Cardiomyopathy Questionnaire
LAD	Left anterior descending
LAVI	Left atrium volume index
LVEF	Left ventricle Ejection Fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MAD	Multiple Ascending Dose
MoP	Manual of Procedures
MPO	Myeloperoxidase
NB	Nota Bene
NO	Nitric Oxide
NYHA	New York Heart Association
o.d	Omni Die *(latin that refers to dosing once daily)*
OAE	other significant adverse event
PCI	Percutaneous Coronary Intervention
PCWP	Pulmonary Capillary Wedge Pressure
PHL	Potential Hy´s Law
PI	Principal Investigator
PK	Pharmacokinetics
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
QoL	Quality of Life
RHI	Reactive hyperemic index
SAD	Single Ascending Dose

Abbreviation or special term	Explanation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of product characteristics
SoA	Schedule of Activities
SoC	Standard of Care
SRC	Safety Review Committee
TBL	Total Bilirubin
TC	Telephone Contact
TDE	Transthoracic Doppler Echocardiography
TE	Target Engagement
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture

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