STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

Protocol/CIP No. D7550C00003

A 12-week, randomized, single-blind, placebo-controlled, multi-centre, parallel group, phase IIa study to evaluate efficacy, safety and tolerability of oral AZD5718 after 4- and 12-weeks of treatment in patients with coronary artery disease (CAD)

Statistical Analysis Plan

Prepared for:
AstraZeneca AB

Final Version 7.0 Date 18MAY2020

VERSION HISTORY OF IMPLEMENTED PLANS

Version	Date	Revision Author	Comments
1.0	18JUL2018	[redacted]	NA
2.0	13NOV2018	[redacted]	Section 6.2.2 – Typo: Table 3 last row Visit 5 was "> last dose + 28". It has been replaced with ">= last dose + 24". Section 6.2.2 – Typo: urine creatinine and Creatinine-normalized uLTE$_4$ has been added in the visit windows section to clarify visit windows also for this derived variable. Section 6.3 – Typo: BMI categories have been adjusted as "Normal <25; Overweight >=25-<=30; Obese >30 kg/m2".

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			Section 6.3 – Typo: the text "The baseline value is the last available value the baseline value used for statistical analyses is the last available value among those in the Baseline visit windows," has been replaced with "The baseline value used for statistical analyses is the last available value among those in the Baseline visit windows," Section 6.3 – Typo: the text ". If the measurement is collected on day 1 but the time of collection (or the planned time point flag) cannot determine if the measurement was before or after the first dose of IP, then it will be considered as collected after the first dose of IP." Has been rephrased for the sake of clarity. Section 6.3 –details on Baseline calculation for PRO questionnaires have been added for the sake of clarity. Section 6.4.2 - Typo: unit of measure for LV longitudinal early diastolic strain rate was (sec). It has been replaced with (s-1). Section 6.6.1 – Typo: the text "If any of the start or stop dates are missing, then imputed dates will not be used, and study drug exposure for that interval will be set to missing; and thus, actual exposure will the sum over only the intervals where drug exposure was not set to missing" has been replaced rephrased for the sake of clarity. Section 6.6.2 – Typo: the text "If the date in which the date of AE became serious is completely missing, the SAE part will be assigned to the AE start phase." Has been replaced with "If the date in which the AE became serious is completely missing, the SAE part will be assigned to the AE phase". Section 6.6.2 – Typo: "SAE part" substituted with "SAE" for the sake of clarity. Section 6.6.2 – Typo: "day" substituted with "date". Section 6.6.2 – Typo: several minor changes on the text about rule of AE and SAE assignation to the study phase for the sake of clarity. Section 6.6.3, 8.8.3, 8.10.3 and section 12 – Urinalysis parameters and the relative statistical analysis have been aligned with the clinical study protocol version 4.0 Section 6.6.4: details on ECG Last observation on-treatment definition have been added for the sake of clarity.

			Section 6.9.1 – Typo: the text "For the purpose of the analysis, only data from subjects with at least 2 acceptable measurements (quality control=1) will be used." Has been replaced with "For the purpose of the analysis, only acceptable measurements (quality control=1) will be used". Section 7.1 – rounding rules for statistical summaries have been changed with the aim to produce more readable outputs. Section 7.3 – imputation rules for first and last date of study drug intake have been changed with the aim to consider multiple delivering of the study drug Section 7.3 - Typo: "With regard to the AE become serious date, if after applying all these rules the imputed AE become serious date is missing or before the AE start date, than the imputed AE become serious date will be the same as the AE start date" has been added in the imputation rules Sections 8.6.1, 8.6.2, 8.7.1, 8.7.2, 8.7.4, 8.10.2, appendix 2 and appendix 3 – It has been added that the statistical models (MMRM) must include also data from visit 4c when comparing variables at visit 4 at the second interim analysis and at the final analysis. Section 8.10.2, appendix 3 – the LVEF tables have been added at interim analyses Section 8.10.2 - Typo: the text "The change from baseline for Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)." Has been replaced with " The change from baseline for Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide) will be analysed using the MMRM model described in section 7.1 with data from visit 2, 3 and 4 at the first IA and data from visit 2, 3, 4 and 4c at the second IA". Section 8.10.2 & 8.10.3 – Specification on reporting only data up-to visit 4 for the first interim analysis and up-to visit 4c for the second interim analysis for all efficacy and safety tables.
3.0	07JAN2019	[redacted]	Section 8.10.3 – added table 11.3.2.1 to the Interim analysis outputs
4.0	16MAY2019	[redacted]	Section 5.2 – Changes to planned analyses added to specify the documentation for the interim analyses and the fact the unblinding team is not involved in the SAP updates after the first interim analysis.

			Section 6.1, Section 6.2.2 – Analysis visit windows adapted to visit windows reported in the CSP version 5.0 Section 6.6.2 – AE occurring during the on-treatment phase and becoming serious during the off-treatment phase will be considered as serious from the on-treatment phase onwards. Section 8.8.2 & Section 12 – added that FDAAA1 tables will be produced as a separate pdf output but delivered at the same time as the CSR outputs. FDAAA1 also renamed in TOC. Section 8.4 & Section 12 – added Appendix 16.2.4.2 - Alcohol use Section 8.10 – updated to prepare second IA. Appendix 2 – added testsvalue=ln(0.2) to the SAS code of the Mixed Model with Repeated Measures (MMRM) – primary and first secondary endpoints (change at visit 4 and 4c on Creatinine normalized $uLTE_4$). Appendix 3 – updated to be consistent with updated section 8.10. Section 12 – numbering updated to be consistent with CSR sections.
5.0	11JUL2019		Section 6.2.2 – Windowing updated to consider measurements after last dose at Visit 4 and Visit 4c. Section 5.2 updated accordingly.
6.0	17DEC2019		Section 5.2, Section 6.9.2 – SF-36 V2 is described instead of SF-36 V1 (scales named differently). Moreover, missing data handling is detailed and U.S. norm is mentioned. Section 6.2.2, Section 6.2.3 and Section 6.3: ECGs, Vital Signs and Physical examinations collected at day 1 will be considered as baseline measurements as per protocol. Section 6.9.3, Section 8.7, Section 8.7.3 – Sections are rephrased to highlight the fact that GRACE score is analysed at baseline as specified in the protocol. Moreover, GRACE score is briefly described in section 6.9.3. Section 7.2 – Section updated with a sensitivity analysis in case there are 5% discrepancies for the type of MI between eCRF and IWRS data. Section 8.1 – Section specifies which analysis sets will be summarized in the output. Section 8.3.5: PK population detailed to clarify the definition.

			Section 12: Sensitivity analysis outputs added to the list of outputs.
7.0	18MAY2020	[redacted]	Section 5.2: Change to planned analysis updated to highlight that there will be summary statistics of plasma concentrations in the CSR. Moreover, some on phone Visit 5 (Follow-up) replace on-site Visit 5 due to COVID19 situation. Section 6.2.2: Specific analysis visit created for PK measurements. Section 6.5: Details about plasma concentrations below limit of quantification. Section 6.6.3: category added to Leukocyte to be consistent with updated eCRF. The typo about Potential Hy's Law is corrected. Section 6.9.2 and section 9: QualityMetric Health Outcomes TM Scoring software replaced by PRO CoRE software. Section 6.9.3, Section 7.1 and appendix 12: typos corrected and wording updated. Section 8.1: Randomization scheme and batches listing added to the analysis. Section 8.3.5: PK data will be described considering the actual treatment the patient received. Section 8.5: Concomitant medication definition updated to consider the last IP dose date. Section 8.6.2: Correction to consider that other secondary variables are tested for no difference in subjects given AZD5718 [redacted] compared to placebo (and not no increase). Section 8.6.3: Analysis of PK variables added to the SAP including summary statistics and listing of plasma concentrations.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE	Adverse Event
ACS	Acute Coronary Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoB	Apolipoprotein B
ApoA1	Apolipoprotein A1
APTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Chemical Classification System
AST	Aspartate aminotransferase
AV-block	Atrioventricular block
AZ-Rand	AstraZeneca randomization solution
BP	Blood pressure
BMI	Body Mass Index
bPWA	Brachial Pulse Wave Analysis
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CBFV	Coronary Blood Flow Velocity
CCS	Canadian Cardiovascular Society grading of angina pectoris
cfPWV	Carotid-femoral Pulse Wave Velocity
CFR	Coronary Flow Reserve
CFVR	Coronary Flow Velocity Reserve
CKD	Chronic Kidney Disease
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form (electronic/paper)
CI	Confidence Interval
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DCCT	Diabetes Control and Complications Trial
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EF	Ejection Fraction
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EoT	End of Treatment
5-LO	5-lipoxygenase
EQ-5D-5L	EuroQol Group (a 5-dimensional, standardised instrument for use as a measure of health outcome applicable to a wide range of health conditions and treatments.)
FLAP	5-lipoxygenase activating protein

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FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Circumferential Strain
GDF15	Growth/differentiation factor 15
GLS	Global Circumferential Strain
GRACE	Global Registry of Acute Coronary Events
GeoMean	Geometric mean
HbA1c	Haemoglobin A1c (glycated haemoglobin)
HBsAg	Hepatitis B surface antigen
Hb	Haemoglobin
HCT	Haematocrit
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HR	Heart Rate
hsCRP	High-sensitivity C-Reactive Protein
hsTnI	High-sensitive Troponin I
IASAP	Interim Analysis Statistical Analysis Plan
ICF	Informed Consent Form
IPD	Important protocol deviations
ICH	International Conference on Harmonisation
ITT	Intention To Treat
IFCC	International Federation of Clinical Chemistry
IL-1B	Interleukin 1
IL-6	betaInterleukin 6
INR	International Normalized Ratio
IP	Investigational Product
[redacted]	[redacted]
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAD	Left Anterior Descending artery
LCX	Left Circumflex Artery
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
LoQ	Limit of quantification
Lp(a)	Lipoprotein a
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LSmean	Least square mean
LSLV	Last Subject Last Visit
log	Logarithmic
LIMS	Laboratory Information Management System
LTB4	Leukotriene B4
LTE_4	Leukotriene E4
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

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MI	Myocardial Infarction
MMRM	Mixed Model with Repeated Measures
MCS	Mental Component Summary
min	Minimum
max	Maximum
MoP	Manual of Procedures
MPO	Myeloperoxidase
MPO mass	Myeloperoxidase protein level measurement
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-Terminal Prohormone of Brain Natriuretic Peptide
n	Number of subjects
NYHA	New York Heart Association's classification
OAE	Other Significant Adverse Event
PCI	Percutaneous coronary intervention
PCS	Physical Component Summary
PD	Pharmacodynamics
PI	Principal Investigator
PP	Per Protocol
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
PT	Preferred Term
PTM	Placebo to Match
Q1	First quartile
Q3	Third quartile
RBC	Red Blood Cell
RCA	Right Coronary Artery
REML	Restricted Maximum Likelihood approach
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SF-36	Short Form (36) Health Survey
SD	Standard Deviation
SMAD	Single and Multiple Ascending Dose
SOC	System Organ Class
SRC	Safety Review Committee
STEMI	ST Elevation Myocardial Infarction
SP (POW)	Spatial Covariance Structures (Power)
TIMI	Thrombolysis In Myocardial Infarction
TDE	Transthoracic Doppler Echocardiography
UK TTO	United Kingdom time trade-off valuation technique
u-	urine
ULN	Upper Limit of Normal
UK - UKN - UKUN	unknown
U.S.	United States
WBC	White blood cell
WBDC	Web Based Data Capture
WHO	World Health Organisation

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2. INTRODUCTION

This Phase IIa Proof-of-Principle study will investigate if AZD5718 can decrease u-LTE_4 levels and secondly if AZD5718 can improve Coronary Flow Velocity Reserve (CFVR) as a measure of myocardial microvascular function. For full details please refer to section 1.1 of the protocol.

This statistical analysis plan (SAP) is based on the final protocol version 5 dated 11Feb2019, the Echocardiography Protocol dated 28May2018, and the SphygmoCor study manual dated 11Jun2018. The SAP includes detailed procedures for executing the statistical analysis related to the primary, secondary, safety and explorative objectives of the study, with the exception of the Pharmacokinetics (PK)/ Pharmacodynamics (PD) modelling which will be described in a separate data analysis plan. In addition, the process for the conduct of the interim analysis will be developed in a separate interim analysis charter.

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

3. STUDY OBJECTIVES

The study has 4 main objectives, the primary objective and three secondary objectives. It also includes some other additional secondary and exploratory objectives and safety evaluation.

The primary objective is:

Primary Objective:	**Outcome Measure:**
To assess the pharmacodynamics (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 4 weeks in CAD patients	Percentage change from baseline in levels of u-LTE_4

The secondary objectives of this study are:

Secondary Objectives:	**Outcome Measure:**
To assess the pharmacodynamics (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 12 weeks in CAD patients.	Percentage change from baseline in levels of u-LTE_4
To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 12 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)

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Secondary Objectives:	**Outcome Measure:**
To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 4 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)

Other secondary objectives are:

Other Secondary Objectives:	**Outcome Measure:**
To assess the pharmacokinetics (PK) of AZD5718 after repeated oral dosing at 4 and 12 weeks in CAD patients	Standard model population pharmacokinetic (PK) parameters to be reported in a separate report
To assess the effect of AZD5718 on coronary flow parameters at 4 weeks in CAD patients	Change at visit 4 (4 weeks) from baseline in: – LAD resting mean diastolic flow velocity – LAD hyperaemic flow velocity
To assess the effect of AZD5718 on change in echocardiographic parameters at 4 weeks in CAD patients.	Change at visit 4 (4 weeks) from baseline in: – LV ejection fraction (LVEF) at rest (%) – LV Global Longitudinal Strain (GLS) at rest and at hyperaemia (%) – LV Global Circumferential Strain (GCS) at rest (%) – LV longitudinal early diastolic strain rate (%)

The secondary objective on PK pharmacokinetics is not treated in this SAP.

The safety objective of this study is:

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of AZD5718 in CAD patients	Adverse Events/Serious Adverse Events (AEs/SAEs) Vital signs Clinical chemistry/haematology parameters Electrocardiogram (ECG) assessments

The explorative objectives of this study are:

- To assess the effect of AZD5718 on coronary flow parameters at 12 weeks in CAD patients
- To assess the effect of AZD5718 on change in echocardiographic parameters at 12 weeks in CAD patients.
- To assess the effect of AZD5718 on change in arterial stiffness, by assessment of carotid-femoral pulse wave velocity (cfPWV) and brachial pulse wave (bPWA) analysis at 4 and 12 weeks in CAD patients
- To evaluate the effect of AZD5718 on cardiovascular biomarkers
- To explore if any baseline variables are predictive of changes in any PD, efficacy, safety and tolerability variable related to AZD5718 treatment
- To explore the effect of AZD5718 on changes in patient reported outcomes (PRO) questionnaires at 4 and 12 weeks
- To evaluate GRACE (Global Registry of Acute Coronary Events) 2.0 score in CAD patients
- To explore the relationship between AZD5718 exposure and the efficacy and exploratory endpoints (echocardiographic, coronary flow, PD, pulse wave analysis, cardiovascular biomarkers) at 4 and 12 weeks
- To explore the effect of AZD5718 on change in additional echocardiographic parameters in CAD patients at 4 and 12 weeks
- To collect and store samples for potential current and future exploratory research aimed at exploring biomarkers involved in PK, PD, efficacy, safety and tolerability related to AZD5718 treatment
- Optional: To collect and store samples for potential current and future exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD5718 treatment

4. STUDY DESIGN

4.1 General Design

A summary of the study will be presented here; full details are provided in the protocol. This is a randomized, single-blind, placebo-controlled, parallel-group, multicentre study in subjects with CAD. For full details please refer to section 1.4 of the protocol.

4.2 Discussion of Study Design

A randomized, blinded, parallel-group, multicentre, placebo-controlled study design is standard in Proof-of-Principle studies and is considered the best design to achieve the objectives of the study, from both safety and efficacy perspectives. Full details regarding the rationale for study design, doses and control groups are reported in section 1.2 of the protocol.

4.3 Method of Assignment of Subjects to Treatment Groups

A centralized (IRT) randomization schedule will be generated by [redacted] using the AstraZeneca randomization solution (AZRand). Subjects will be randomized in a ratio 2:1:2 to receive either AZD5718 [redacted] AZD5718 [redacted] or Placebo. At randomization the IRT will assign eligible subjects a unique randomization code and blinded

Investigational Product (IP) kit number(s). Block randomization using IRT will be used to randomize subjects in a 6:3:4:2 ratio to receive a fixed dose of AZD5718 [redacted], AZD5718 [redacted] placebo [redacted] or placebo [redacted]

The randomization will be stratified with type of Myocardial Infarction (MI) as a factor (STEMI vs NSTEMI).

4.4 Blinding

The study will have a single blind design. The study is single-blind regarding treatment strengths, but double blind in terms of active or placebo.

No member of the study team at AstraZeneca, or representative, personnel at study centres, or any Clinical Research Organization (CRO) handling data will have access to the randomization scheme during the conduct of the study, with the exception of the [redacted] Informatics personnel generating the randomization scheme as well as AstraZeneca Supply Chain, and the CRO companies conducting PK sample analyses, providing the IRT and carrying out the packaging and labelling of the study medication. This documentation will be kept in a secure location until the end of the study.

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists from the IRT. The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for Serious Adverse Events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented. For the interim analysis, independent personnel with no other involvement in the study will be unblinded to certain data. The process for the conduct of the interim analysis including the unblinding process will be described in a separate interim analysis plan.

4.5 Determination of Sample Size

The study has been powered to show a statistically significant result for the primary endpoint, first, second and third secondary endpoints. To preserve the overall type1-error at 5% when testing these four endpoints a Hierarchical Procedures will be used (Dmitrienko A et al 2006). This procedure implies that one will test the four endpoints in a predefined sequence: test of main objective, test of first secondary objective, test of second secondary objective, test of third secondary objective. The test procedure will stop as soon as the first

none-significant test, one-sided test at a 5% level, occur and all following test will be declared as none-significant.

The Hierarchical testing sequence for the four endpoints are:

1. Change from baseline in Creatinine-normalized u-LTE_4 at 4 weeks
2. Change from baseline in Creatinine-normalized u-LTE_4 at 12 weeks
3. Change from baseline in CFVR at 12 weeks
4. Change from baseline in CFVR at 4 weeks

Data from MAD study shows inhibition of u-LTE_4 by AZD5718 [redacted] can be assumed to be log-normally distributed, with an expected inhibition of u-LTE_4 of approximately 96% and a standard deviation of <4%. Patients given placebo are expected to have no inhibition of u-LTE_4 with the same standard deviation (on the logarithmic scale) as patients given AZD5718 [redacted] Given this, 33 evaluable patients in the AZD5718 [redacted] group and 33 evaluable patients given placebo will be sufficient to achieve > 99% power to show a statistically significant inhibition of u-LTE_4 of at least 80%, using a one-sided confidence interval of 95% at week 12.

Assuming a log-normal distribution of the CFVR and an expected 20% increase in CFVR in the AZD5718 [redacted] group compared to placebo with a coefficient of variation (CV) of 30%, 33 evaluable patients per arm is required to achieve 80% power with a one-sided confidence interval of 95%.

About 40 randomized patients per arm (AZD5718 [redacted] or placebo) treated for 12 weeks is needed to account for non-evaluable patients (approximate 18% dropout).

For supporting dose selection in future studies, a treatment arm with about 20 randomized patients receiving AZD5718 [redacted] for 12 weeks is included in the study, in order to get 17 evaluable patients. The number of 17 subjects has been deemed to provide sufficient exposure-response information.

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

This SAP is implemented based on CSP v5.0 dated February 11, 2019.

5.1 Changes in the Conduct of the Study

No changes respect to the CSP v5.0 dated February 11, 2019 are present.

5.2 Changes from the Analyses Planned in the Protocol/CIP

- Protocol Section 8.5 states that geometric mean and CV will be presented for all efficacy and safety variables. However, these will be presented only for log-normal variables as deemed not relevant for all the other variables.

- Protocol section 8.5.3 refers to changes from baseline in Electrocardiogram (ECG) parameters. Only the overall ECG evaluation will be summarised.
- Protocol refers to evaluable subjects as subjects with valid CFVR measurements at Visit 2 (baseline), and one postbaseline visit as judged by the CFVR Core lab. However, CFVR Core lab will flag the validity of the measurements for the single visit. Then, the evaluability of the subject will be stated based on the validity of the 2 measurements, at Visit 2 and at one postbaseline visit.
- Protocol section 8.5.3 states that 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. However as per standard AZ, the frequency of changes with respect to normal ranges will be tabulated between baseline and worst case registered (minimum or maximum) during treatment.
- Protocol section 8.5.3 states that shifts from normal to abnormal between baseline and end of treatment time point will be evaluated for urinalysis. However as per standard AZ TOC, shifts for urinalysis will be based on the modalities of the variables.
- Protocol section 5.2 stated that Serology (Human immunodeficiency virus (HIV) I and II, Hepatitis B surface Antigen (HBsAg), Hepatitis C virus antibody), and for females only FSH (mIU/ml) and LH (IU/L) will be performed at a local laboratory for screening only. However, these variables are not recorded in the CRF and will not be analysed.
- Protocol section 3.5 stated that IWRS/IVRS will assign eligible patients a unique randomization code and blinded investigational product (IP) kit number(s) to the patient; However, IWRS/IVRS will be replaced with IRT.
- Protocol section 8.3.1 stated that the efficacy analysis set will include all patients who were randomised, received at least one dose of study medication and have at least one baseline or postbaseline measurement. However, here it will have specified that this population will include all patients who were randomised, received at least one dose of study medication and have at least one baseline or postbaseline measurement for at least one of the efficacy variables (including all, primary secondary or exploratory variables).
- Protocol section 8.5.6 stated that an interim analysis plan will be prepared and finalized prior to the first administrative interim analysis. However, this interim analysis plan is based on a dedicated section of the SAP and there will be an update of the interim analysis charter before the second interim analysis.
- Protocol section 8.1 stated that any subsequent amendments to the SAP will be documented, with final amendments completed prior to unblinding of the data for the analysis. But it should be added that unblinded team will not be involved in any SAP amendment which will take place after the first unblinding for the first interim analysis.
- Protocol section 4.1 stated that CFVR measurement should be done before the IP intake during the visit. In the SAP, measurements done 3 days after last dose can be considered as the visit measurement.
- Protocol section 5.3.2 included a brief description of the question SF-36 V1 while V2 is used in the study. The wording was updated in the SAP to be consistent with the questionnaire SF-36 V2.

- Protocol section 2.2 stated that standard model population PK parameters would be reported in a separate report. However, plasma concentrations will be part of the CSR and PK parameters described in a separate report.
- Protocol section 4.1 described an on-site Visit 5 (Follow-up). However, due to COVID19 situation, some phone visits replaced on-site visits. Protocol deviations were reported for each patient in that situation.

6. BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

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

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Table 2: Study assessment schedule

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
Informed consent (ICF)		x							
Inclusion/exclusion criteria		x	x						
Demographic data		x							Smoking history and alcohol consumption to be included
Height		x							
Body weight[b]		x	x	x	x		x	x	
Collect date for ACS event		x							
TIMI flow score		x							
Medical and surgical history		x							

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	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
Concomitant medication		x	x	x	x	x	x	x	
Serology		x							
FSH and luteinizing hormone (LH) sampling (females only)		x							
Randomization			x						
Diary card hand-out			x						
Diary card review				x	x	x	x		
Diary card hand-in							x		
IP dispensed			x		x	x			
IP returned					x	x	x		

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
IP intake at the clinic			x	x	x		x		
Safety and tolerability:									
Adverse event (AE) review		x (SAE only)	x	x	x	x[m]	x	x	
Blood pressure and pulse rate (supine)		x	x	x	x		x	x	
12-lead pECG with electronic source file		x	x	x	x		x	x	
Physical examination[c]		x	x	x	x		x	x	

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
Blood and urine samples for safety laboratory evaluations (including fasting glucose)[d]		x[e,n]	x[f]	x[n]	x		x	x	
Efficacy Assessments:									
Spot urine for analysis of LTE_4 levels and urinary creatinine		x[l]	x[g]	x (pre-dose)	x (pre-dose)		x(pre-dose)	x	Screening sample will not be used for assessment of primary endpoint
CFVR measurement			x		x		x		

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
Echocardiography			x		x		x	x	
cfPWV/bPWA			x		x		x	x	
Pharmacokinetics:									
Plasma for AZD5718			x[h]	x[i]	x[j]		x[i]	x[k]	
Exploratory Clinical Variables:									
-PRO questionnaires			x (post-dose)		x (post-dose)		x (post-dose)		
-GRACE 2.0 Score		x							
Exploratory Biomarkers:									

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
-Plasma for analysis of LTB_4 levels		x[1]	x (pre-dose)	x (pre-dose)	x (pre-dose)		x (pre-dose)	x	
-Blood samples for cardiovascular biomarkers		x[1]	x (pre-dose)	x (pre-dose)	x (pre-dose)		x (pre-dose)	x	
-Plasma samples to be stored in biobank for exploratory analyses		x[1]	x (pre-dose)	x (pre-dose)	x (pre-dose)		x (pre-dose)	x	
-Optional Genetic sampling			x[o]						

a Screening during in-house stay after Acute Coronary Syndrome (ACS) event. Assessments can take place over several days. If the patient is discharged from hospital early, he/she may be asked to come back for blood sampling.

b Body weight assessments to be conducted in the mornings after an overnight fast, except for non-fasting at screening (Visit 1)

c Full physical examination at Screening (Visit 1) and at Follow-up (Visit 5), and brief physical examination on the other occasions (Visits 2, 3, 4 and 4c).

d Fasting plasma samples for glucose measurements to be obtained after an overnight fast (from 10 p.m. the evening before) at the same time point at Visits 2, 3, 4, 4c and 5 to the extent possible.

e Will exclude fasting glucose measurement.

f Liver panel analyses results will be used for assessment of exclusion criteria. Samples need to be analysed as acute samples.

g Spot urine sample to be collected in the morning prior to screening and baseline assessments.

h Baseline sample to be obtained in the morning before screening assessments. The other sample to be taken between 1-8 h post-dose.

i C_{Trough} sample to be collected before dose administration at 20-28 hours after previous dose (dose on day 13 (day before Visit 3) and on day before Visit 4c).

j Sampling times: pre-dose and then 0-2 h, 2-4 h, 4-8 h post dose. Sampling will be separated with at least 1 hour.

k One PK-sample to be collected as suitable in relation to the other follow-up measurements. Exact sampling time to be entered in the CRF.

l Sampling, where feasible, at 1, 2, 3 and 5 days post ACS. Exact sampling time to be entered in the CRF.

m Unscheduled safety assessments (blood and urine samples for safety lab and ECG) may be performed as judged by the investigator.

n Will exclude TSH, Free T3, Free T4 and Total T4.

o The genetic sample may be collected at any time after randomization, however, ideally samples should be collected at Visit 2.

Order of assessments:

1. Spot urine sample for LTE_4 (u-LTE_4)
2. Safety labs, ECG, AE-review, physical examination and vital signs
3. Echocardiography, cfPWV/bPWA, (Vis 2, 4, 4c and 5) CFVR (Vis 2, 4 and 4c)
4. Sampling for Exploratory biomarkers and PK
5. Intake of IP
6. Meal
7. Post-dose PK sample no. 1 (Vis 2 and 4)
8. PRO (Vis 2, 4 and 4c)
9. Post-dose PK sample no. 2 (Vis 4)
10. Post-dose PK sample no. 3 (Vis 4)

Details on study procedures are reported in section 4.1 of the protocol.

6.2 Time Point Algorithms

6.2.1 Relative Day

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

- For days on or after the first dose of study drug: Date of Assessment – Date of First Dose of IP + 1.
- For days before the first dose of study drug: Date of Assessment – Date of First Dose of IP.

6.2.2 Windows

For the purpose of statistical analysis and if not otherwise specified, all the efficacy variables (primary, secondary and exploratory variables) and all the safety variables (Clinical laboratory evaluations, ECGs, Vital Signs and Physical examinations) will be assigned to the visit in which they are collected depending on the following analysis visit windows.

Table 3: Visit windows

Analysis visit (AVISIT)	Scheduled visit day	Visit Window for Analysis (Days)
Baseline[b]	1	<1[a]
Baseline Post-dose[c]	1	1
Visit 3	14	10 – 18 and <= last dose
Visit 4	28	23 – 33 and <= last dose + 3
Visit 4b	56	49 – 63 and <= last dose
Visit 4c	84	74 – 94 and <= last dose + 3
Visit 5 – FUP 1 month	56 / 112	> =last dose + 24

[a] Includes also measurements collected at day 1 prior to first dose of IP for all variables except PRO questionnaires, ECGs, Vital Signs and Physical examinations. For PRO questionnaires, ECGs, Vital Signs and Physical examinations, all the measurements collected at day 1 will be considered as baseline measurements as per protocol. For uLTE$_4$ and cardiovascular biomarkers, the baseline will be the last available value before the first dose of treatment, among the values collected after the ACS event +7 days (included).

[b] Analysis visit will be labelled "Baseline Pre-dose" for PK measurements.

[c] Only applicable to PK measurements occurring on Day 1 after the first dose.

Measurements collected outside the visit windows will be labelled as "Unscheduled visit". For uLTE$_4$, urine creatinine, Creatinine-normalized u-LTE$_4$ and Cardiovascular biomarkers, measurements collected from date of ACS event to 6 days post ACS will be labelled as "Screening".

In general, the baseline value used for statistical analyses is the last available value among those in the Baseline visit windows, prior to first dose of IP, except for PRO questionnaires. Additional details for baseline assessment will be given in section 6.3.

For visit windows 3, 4, 4b, 4c and 5 if more than one measurement of the variable (scheduled or unscheduled visit) falls in the same visit window but in different days, the nearest to the scheduled visit day will be taken. If several measurements are collected within the same distance from the scheduled study day, the data of the latest visit after the scheduled study day within that window will be used.

If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements will be taken. For numeric values, the analysed value will be the arithmetic mean for normal distributed variables and the geometric mean for log-normal distributed variables.

6.2.3 Phase

For the purpose of safety analyses, analysis phase will be defined in terms of study days since the first day of the study medication, as illustrated in the following table:

Table 4: Analysis phases

Phase	Phase Window for Analysis (Days)
Baseline phase	before first dose of study IP (day <1[a])
On-treatment phase	From day 1[b] to ≤ 7 days after last dose of study drug
Off-treatment phase	>7 days after last dose of study drug

[a] Includes all measurements collected before first dose of IP. If the measurement is collected on the day of first dose of IP but the time of collection (or the planned timepoint) cannot determine if the measurement was before or after first dose of IP, then it will be considered as collected after first dose of IP except for ECGs, Vital Signs and Physical examinations which are considered as pre-dose measurements as per protocol.

[b] Includes all measurements collected on the day of first dose of IP (Day 1), at the time of IP intake and after.

6.3 Baseline Assessments

The baseline value used for statistical analyses is the last available value among those in the Baseline visit windows, prior to first dose of IP, except for PRO questionnaires. As reported in the footnote (a) of table 4, if the measurement is collected on day 1 but it cannot be determined if the measurement was done before or after the first dose of IP (due to missing time or planned time point flag or missing time of first dose of IP), then it will be considered as collected after the first dose of IP. There is one exception to that for ECGs, Vital Signs and Physical examinations which are considered as pre-dose measurements as per protocol. If several measurements are collected on the last date (same day) prior to the first day of IP, or on the first day of IP prior to the first dose, the baseline value will be the average (for numeric values)/worst (for categorical values) of the measurements.

For uLTE$_4$ and cardiovascular biomarkers, screening measurements (from ACS event to 6 days post ACS event included) cannot be used as baseline values. For these variables the baseline will be the last available value before the first dose of treatment, among the values collected after the ACS event +7 days (included). If the measurement is collected on day 1 but it cannot be determined if the measurement was done before or after the first dose of IP (due to missing time or planned time point flag or missing time of first dose of IP), then it will be considered as collected after the first dose of IP. If several measurements are collected on the last date (same day) prior to the first day of IP, or on the first day of IP prior to the first dose, the baseline value will be the average of the measurements.

For PRO questionnaires, the baseline is the value collected before or on day 1. If several measurements are collected on the same day, the baseline value will be the average of the measurements.

The following will be evaluated as baseline assessments at visit 1 (screening visit):

- Demographics (age (years), age group (<50; >=50 -<65; >=65 years), race, ethnicity, sex, weight (kg), weight group (<70; >=70- <90; >=90 kg), height (cm), BMI (kg/m2), BMI group (Normal <25; Overweight >=25-<=30; Obese >30 kg/m2) and country.
- Relevant medical and surgical history
- Specific medical and surgical history
- Nicotine use and alcohol use, consumption and frequency
- Allowed concomitant medications

6.4 Efficacy Variables

6.4.1 Primary Efficacy Variable(s)

Spot urine for analysis of LTE$_4$ levels (pmol/L) and urinary creatinine (mmol/L) will be collected at Visit 1, Visit 2, Visit 3 (pre-dose), Visit 4 (pre-dose), Visit 4c (pre-dose) and Visit 5. Primary efficacy variable is the Creatinine-normalized u-LTE$_4$ (pmol/mmol) which will be calculated as the u-LTE$_4$ / urinary creatinine. If the u-LTE$_4$ value falls under the limit of quantification (LoQ) then creatinine-normalized u-LTE$_4$ will be calculated as the limit/(sqrt(2)*creatinine). LoQ value will stated in the raw data.

The primary efficacy endpoint is the change at visit 4 (4 weeks) from Baseline in creatinine-normalized u-LTE$_4$. The first secondary efficacy endpoint is the change at visit 4c (12 weeks) from Baseline in creatinine-normalized u-LTE$_4$.

Baseline Creatinine-normalized u-LTE$_4$ value is defined as in section 6.3.

Creatinine-normalized u-LTE$_4$ is potential unblinding data. For the interim analysis these data will be provided only to the dedicated Covance unblinded team which will perform the analysis and send the results to the dedicated AZ unblinded team. Further details of the unblinding will be provided in the IA charter. For the final analysis these data will be provided to the Covance blinded team only after the database lock.

6.4.2 Secondary Efficacy Variables

Secondary efficacy variables will be collected at Visit 2, Visit 4 and Visit 4c. The secondary efficacy variables are:

- CFVR (ratio)
- LAD resting mean diastolic flow velocity (m/s)
- LAD hyperaemic flow velocity (m/s)
- Measurements of left ventricular (LV) systolic and diastolic function, more specifically:
  - LV Ejection Fraction (LVEF) at rest (%)
  - LV Global Longitudinal Strain (GLS) at rest and at hyperaemia (%)
  - LV Global Circumferential Strain (GCS) at rest (%)
  - LV longitudinal early diastolic strain rate (s^{-1})

Change at visit 4c (12 weeks) and at visit 4 (4 weeks) from Baseline in CFVR are the second and the third secondary efficacy endpoints respectively.

Change at visit 4 (4 weeks) and at visit 4c (12 weeks) on all other secondary variables will be tested as other secondary endpoints and exploratory endpoints respectively.

Baselines are defined as described in section 6.3.

For the CFVR only valid measurements will be used for the analysis. Valid measurement at each visit will be defined by the CFVR Core lab by means of a validity flag in the raw dataset (EVALPAT = Valid).

For all the other variables if images are not presented/not measurable, they are considered NOT VALID. If measurable, they are graded as POOR/ACCEPTABLE/GOOD depending on quality. All data except NOT VALID should be analysed.

6.4.3 Additional Efficacy Variables

Not Applicable.

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

Venous blood samples for the determination of plasma concentrations of AZD5718 will be collected at the time points presented in the study assessments schedule. Standard model population PK parameters will be reported in a separate report.

Plasma concentrations below the limit of quantification (LoQ) after first dose of IP will be set to LoQ/2.

6.5.1 Handling of Pharmacokinetic Parameter Outliers

Not applicable.

6.6 Safety Assessments

Safety assessments include AEs, clinical laboratory safety evaluations (haematology, serum biochemistry and urinalysis), vital signs (blood pressure, pulse rate and pulse oximetry), physical examination and 12-lead ECG.

6.6.1 Extent of Exposure and Compliance to Study Treatment

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

- Visit 2 (Randomization),
- Visit 4 (4 weeks),
- Visit 4b (8 weeks).

Dose at Visit 2 (day 1), Visit 3 (day 14), Visit 4 (4 weeks) and Visit 4c (week 12) will be given by study personnel at the study site. The exact dose intake time before Visit 3, Visit 4 and Visit 4c will be recorded on a Diary Card. The 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.

Exposure and compliance are calculated as follow:

Exposure

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

Actual exposure (days) will be calculated as the total number of days of effective study drug intake (i.e., gaps in dosing due to study drug interruption will be taken-out from the calculation). In this way, the subject's dosing can be reduced to a series of unbroken intervals within each of which exposure will be calculated as study drug dose stop date minus the study drug dose start date plus one. Actual exposure will be calculated as the sum of exposures over all the unbroken intervals.

If any of the start or stop dates are missing for an interval, study drug exposure for that interval will be set to missing. Imputed dates on first and last dose will not be used. Actual exposure will be the sum over only the intervals where drug exposure was not set to missing.

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

- >= 7,
- >= 14,

- >= 28,
- >= 56,
- >= 84.

Compliance

During the single-blind treatment period, subjects are supposed to take [redacted] once daily if on high dose and [redacted] once daily if on low dose of AZD5718 or matching placebo according to the dosing schedule. Overall compliance to the dosing schedule will be examined for subjects in the Safety Analysis Set.

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

- (Total number of tablets consumed) x 100 / [(Exposure) x 2] for subjects on [redacted] of AZD5718 or matching placebo and
- (Total number of tablets consumed) x 100 / (Exposure) for subjects on [redacted] of AZD5718 or matching placebo

where, total number of tablets consumed will be calculated as: Total number of tablets dispensed – Total number of tablets returned. The quantity of study drug dispensed to and returned by the subject will be counted and recorded on the drug accountability eCRF page.

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

Compliance will also be computed using the following categories:

- < 80%
- ≥ 80% to < 120%
- ≥ 120%

6.6.2 Adverse Events

Adverse Events (AE) will be collected from time of the first dose throughout the treatment period and including the Off-treatment phase (see section 6.2.3 for the phase definition). SAEs will be recorded from the time of informed consent.

After the imputation of AE start date and AE end date as described in section 7.3, AEs will be assigned to the period where they start according to the following algorithm:

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

- If the AE starts prior to the first dose of IP, then the AE will be assigned to the Baseline phase
- If the AE starts on or after the first dose of IP through 7 days after the date of the last dose of IP (inclusive), then the AE will be assigned to the On-treatment phase,

- If the AE starts after the date of last dose of IP + 7 days (not inclusive), then the AE will be assigned to the Off-treatment phase.

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

- If the AE starts prior to the date of the first dose of IP, then the AE will be assigned to the Baseline phase,
- If the AE starts on or after the date of the first dose of IP through 7 days after the date of last dose of IP (inclusive), then the AE will be assigned to the On-treatment phase,
- If the AE starts after the date of last dose of IP + 7 days (not inclusive), then the AE will be assigned to the Off-treatment phase.

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

- If the end-date is known:
  - If the end-date is before the date of first study IP then the AE will be assigned to the Baseline phase
  - If the end-date is on or after the date of first IP, no assignation can be done.
- If the end-date is completely missing no assignation can be done

The way the SAEs will be assigned to a specific period will be different for the first IA and second IA/final analysis.

First IA considerations

After the AE allocation to corresponding study phase, also the AE seriousness part of the event will be allocated to the corresponding study phase by means of the date in which the AE becomes serious.

After the imputation of the AE becomes serious as described in section 7.3, the SAE will be assigned to the period where it starts according to the following algorithm:

- If the date in which the AE becomes serious is prior to the date of the first dose of IP, then the SAE will be assigned to the Baseline phase,
- If the date in which the AE becomes serious is on or after the date of the first dose of IP through 7 days after the date of last dose of IP (inclusive), then the SAE will be assigned to the On-treatment phase,
- If the date in which the AE becomes serious is after the date of last dose of IP + 7 days, then the SAE will be assigned to the Off-treatment phase.

If the date in which the AE became serious is completely missing, the SAE will be assigned according to the AE start date and time.

The SAE assignation is used only to identify cases in which the AE starts as Non-serious in the On-treatment phase and becomes Serious in the Off-treatment phase. In cases like these, the AE will be reported as one single AE in the listings, but it will be summarized as one non-serious AE in the On-treatment tables and one SAE in the Off-treatment tables.

Second IA and final analysis considerations

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

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

The coding dictionary for this study will be the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

6.6.3 Clinical Laboratory Evaluations

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (see section 6.1).

The following laboratory variables will be measured at local lab:

Table 5: Clinical Laboratory Evaluation Panels

Haematology/Haemostasis (whole blood)	White blood cell (WBC) count Red blood cell (RBC) count Haemoglobin (Hb) Haematocrit (HCT) Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) Neutrophils absolute count Lymphocytes absolute count Monocytes absolute count Eosinophils absolute count Basophils absolute count Platelets Reticulocytes absolute count
Coagulation	International normalized ratio (INR) Activated partial thromboplastin time (APTT) Fibrinogen
Clinical Chemistry* (serum or plasma)	Sodium

	Potassium
	Urea
	Creatinine
	Albumin
	Calcium
	Phosphate
	Glucose (fasting) (Not at Visit 1 - Screening)
	Alkaline phosphatase (ALP) "LIVER PANEL"
	Alanine aminotransferase (ALT) "LIVER PANEL"
	Aspartate aminotransferase (AST) "LIVER PANEL"
	Total bilirubin "LIVER PANEL"
	TSH
	Free T3
	Free T4
	Total T4
Urinalysis	Glucose (dipstick)
	Albumin (quantification/semi-quantification)
	Protein (dipstick)
	Blood (dipstick)
	WBC (Leukocytes) (dipstick)
	Creatinine (quantification)

*In case that ALT, AST>2ULN, ALP increase by 100%, bilirubin (total)>1.5ULN, intensified and extensive liver panel will be conducted.

Conversions to AZ preferred units will be applied where needed. Units and conversion factors are reported in the "Labcodes" version dated 16 May 2017 or higher. Laboratory measurements will be considered on treatment if they are collected from Day 1, after first dose of IP up to 7 days after the last dose of IP. Baseline value is defined in section 6.3.

Laboratory values will also be classified as normal (if value is within normal reference range) low (if value is below the low normal reference limit) or high (if value is above the high normal reference limit).

Potential Hy's law criteria will be assessed by total bilirubin, ALT and AST, as follow:

Parameter	Criteria
Total bilirubin	< 2xULN

	≥ 2xULN
	Total
ALT	< 3xULN
	≥ 3 - < 5xULN
	≥5 - < 10xULN
	≥10xULN
	Total
AST	< 3xULN
	≥ 3 - < 5xULN
	≥5 - < 10xULN
	≥10xULN
	Total

Subject's highest on-treatment value will be used. Potential Hy's Law criterion is defined 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. 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.

Urinalysis categorical variables will be classified as:

Parameter	Criteria
Glucose	Neg
	1+
	2+
	3+
	4+
Albumin	0
	1+
	2+
	3+
	4+
	Trace
Protein	Neg
	Trace
	+1
	+2
	+3
	+4
Blood	Neg
	Non-hem Trace
	Non-hem 2+
	Hem Trace
	Hem 1+
	Hem 2+

	Hem 3+
WBC (Leukocytes)	Neg 1+ 2+ 3+ 4+

6.6.4 Other Observations Related to Safety

Other observations related to safety will include Vital Signs, Electrocardiogram (ECG), Physical examinations, Body weight and BMI. Baseline values are defined as in section 6.3. Recordings are considered on treatment if they are collected from Day 1, after first dose of IP up to 7 days after the last dose of IP.

Vital Signs

Vital signs will include:

- Pulse rate (bpm),
- pulse oximetry (%),
- systolic blood pressure (mmHg),
- diastolic blood pressure (mmHg).

Vital signs will be obtained at time points indicated in section 6.1 (and ad-hoc as medically indicated). Pulse (beats/minute, radial artery, during 30 seconds) and pulse oximetry (%) will be measured before blood pressure and in a lying position after 10 minutes of rest. Thereafter, systolic and diastolic blood pressure (mmHg, the cuff method on the arm opposite to the one used for blood sampling) will be measured using the same cuff, appropriate for arm circumference, and in the same position, throughout the study. Subjects should be in the same position for the vital signs measurements throughout the study.

Change from baseline to each post-baseline measurement will be calculated as the post-baseline visit value minus the baseline visit value.

Electrocardiogram (ECG)

12-lead ECG recordings will be collected according to the assessments schedule presented in section 6.1. The investigator will make an overall evaluation of the ECG as normal, abnormal, abnormal non-clinically significant and abnormal clinically significant. Abnormal values shall not be recorded as AEs unless deemed clinically significant. Last observation on-treatment used for statistical analyses is the last available value among those in the On-treatment phase. If several measurements are collected on the last date (same day), the last on-treatment value will be the worst of the measurements collected during that day.

Physical Examination

A complete physical examination will be performed at Screening (Visit 1) and at Follow-up (Visit 5) 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, musculoskeletal (including spine and extremities) and neurological systems. On the other occasions (Visits 2, 3, 4 and 4c) a brief physical examination (general appearance, skin, abdomen and musculoskeletal, cardiovascular and respiratory systems) will be conducted. 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.

Physical examination will be determined by the investigator as normal, abnormal non-clinically significant and abnormal clinically significant.

Body Weight and BMI

Body weight and BMI will be collected according to the assessments schedule presented in section 6.1. Body weight assessments will be conducted in the mornings after an overnight fast (except for non-fasting at screening) with the subjects in underwear/light clothes and after a lavatory visit. Assessments are to be done on the same calibrated scale at all occasions. BMI is collected at screening only. For the purpose of the analyses BMI will be derived at each visit as: weight (kg) at visit / [height (m) at screening]^2, rounded to two decimal places.

Change from baseline to each post-baseline measurement will be defined as the post-baseline visit value minus the baseline visit value.

6.7 Pharmacodynamics Parameters

Not applicable

6.8 Research Biomarkers

Samples for determination of cardiovascular biomarkers (Table below) will be taken at the times presented in the study assessments schedule, section 6.1. Cardiovascular biomarkers are reported in the following table.

Table 6: Cardiovascular biomarkers

Panel Name	Biomarkers
Cardiovascular Biomarkers	Lipid profile (total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol, (HDL-C), triglycerides)*
	hsTnI (high sensitive Troponin I) (ng/mL)
	hsCRP (High-sensitivity C-Reactive Protein) (mg/dL)
	NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide) (pmol/L)
	Lp(a)* (Lipoprotein a)
	ApoA1* (Apolipoprotein A)
	ApoB*

*Analysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Conversions to AZ preferred units for cardiovascular biomarkers performed at local laboratories will be applied where needed. Units and conversion factors are reported in the "Labcodes" version dated 16 May 2017 or higher. Other cardiological biomarkers and responder analysis of PD biomarkers, as well as genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD5718 treatment will be referred in an exploratory SAP and results will be described in a separate report.

The exploratory endpoints concerning cardiovascular biomarkers are the change at visit 4 (4 weeks) and at visit 4c from Baseline. Baseline value is defined as in section 6.3.

6.9 Exploratory Variables

6.9.1 Carotid-femoral pulse wave velocity and brachial pulse wave analysis

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

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

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

For the purpose of the analysis, only acceptable measurements (quality control=1) will be used. The average per visit for cfPWV/bPWA parameters will be calculated as follows:

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

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

(Brachial blood pressure systolic – Brachial blood pressure diastolic)/(Central blood pressure systolic – Central blood pressure diastolic). Note that central blood pressure systolic cannot physiologically equal central blood pressure diastolic; thus, the denominator cannot

equal 0. If one of the values used for calculating pulse pressure amplification is missing, then pulse pressure amplification will be missing.

The exploratory endpoints concerning cfPWV/bPWA are the change at visit 4 (4 weeks) and at visit 4c from Baseline. Baseline value is defined as in section 6.3.

6.9.2 Clinical Outcome Assessments

The following PRO questionnaires will be collected at the times presented in the study assessments schedule, section 6.1:

- SF-36 V2.
- EQ-5D-5L from EuroQol Group
- Rose Dyspnoea score
- FACIT-Fatigue scale

The exploratory endpoints for PRO questionnaires are the changes at visit 4 (4 weeks) and at visit 4c (12 weeks) from Baseline. Changes are calculated as the Visit value minus the Baseline value. Baseline is defined as described in section 6.3. The PRO questionnaires variables are described below:

SF-36 V2

SF-36 is a general well-validated questionnaire which encompasses eight health domains:

1. physical functioning,
2. role physical,
3. bodily pain,
4. general health,
5. vitality
6. social functioning,
7. role-emotional,
8. mental health.

It also includes a single item that provides an indication of perceived change in health called Reported Health Transition (item 2 "Compared to 1 week ago, your health now"). In addition, 2 component summary measures, a physical component summary (PCS) measure and a mental component summary (MCS) measure will be constructed and scored based on the 8 health domain scales.

Scoring the data for the 8 health domains and the 2 component summaries will be performed using PROC CoRE Software 1.5. The software uses 2009 U.S. population norms and applies a Missing Data Estimation method as follows:

- A health domain score (except the physical functioning domain) will be estimated provided that at least one non-missing response is available within that domain.

- For the physical functioning domain item response theory will be used to develop a model for estimates of the missing score.
- Regression methods are then applied to estimate the PCS and the MCS on the basis of the available domains.

The eight health domains, the perceived change in health and the 2 component summary measures will be included in the statistical analysis.

EQ-5D

The EQ-5D questionnaire has five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression and each dimension has five response levels i.e., level 1=no problem or none; level 2=slight problems; level 3=moderate problems; level 4=severe problems; level 5= unable to perform activity.

Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems

- Level 1: indicating no problem
- Level 2: indicating slight problems
- Level 3: indicating moderate problems
- Level 4: indicating severe problems
- Level 5: indicating extreme problems

The overall EQ-5D index score will be calculated on the basis of the UK set of weights (Euroqol UK TTO - EQ-5D-5L crosswalk index values with SAS using the United Kingdom (UK) value set). There should be only one response for each dimension. Missing values are treated within the Euroqol UK TTO algorithm of calculation. Only the overall EQ-5D index score will be included in the statistical analysis.

Rose Dyspnoea

The Rose Dyspnoea questionnaire has 4 items which need to be answered as Yes (scored 1) or No (scored 0):

- Item 1: Do you get short of breath when hurrying on level ground or walking up a slight hill?
- Item 2: Do you get short of breath when walking with other people your own age on level ground?
- Item 3: Do you get short of breath when walking at your own pace on level ground?
- Item 4: Do you get short of breath when washing or dressing?

Each activity associated with dyspnoea is assigned 1 point. The overall rose dyspnoea score will be calculated as the sum of the 4 scores and will range from 0 to 4, with 0 indicating no dyspnoea with activity and increasing scores indicating more limitations due to dyspnoea. Missing data will be counted as 0. If at least two out of the four items will be missing, then the overall rose dyspnoea will be missing.

Only the overall rose dyspnoea score will be included in the statistical analysis.

FACIT - Fatigue

The FACIT-Fatigue scale is a 13-item questionnaire, and each questionnaire has one of the following responses: Not at all, A little bit, some-what, Quite a bit, Very much.

Responses should be coded as follows:

- Not at all = 0,
- A little bit = 1,
- Some-what = 2,
- Quite a bit = 3,
- Very much = 4.

All responses must be reversed by subtracting the response from "4" except the responses to subscale items 'I have energy' and 'I am able to do my usual activities' which should remain as scored above. All subscale items will be then summed, multiplied by the number of items in the subscale (i.e. 13), and then divided by the number of items answered. This will produce the prorated subscale score. The higher the score the better the quality of life.

If there will be missing data, prorating by subscale in this way will be acceptable as long as more than 50% of the items were answered (e.g., a minimum of 7 of 13 items). If 50% of the items or less are answered, the prorated subscale will be missing. Only the prorated subscale score will be included in the statistical analysis.

6.9.3 GRACE 2.0 score at baseline

GRACE score is an ACS Risk Calculator that provides the percentage probability of death or death/MI at time-points up to 3 years following admission with ACS.

Subjects will be assessed for GRACE 2.0 score (%) at baseline.

7. STATISTICAL METHODS

7.1 General Methodology

Data will be summarized using descriptive statistics, by treatment group which consist of AZD5718 [redacted] AZD5718 [redacted] and placebo, where the placebo group matches the [redacted] and [redacted] doses respectively. Data will be summarized at each visit.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, SD, median, minimum and maximum.

For log-normal variables, descriptive statistics will include n, mean, SD, median, minimum, maximum, geometric mean (GeoMean) and coefficient of variation (CV).

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

For count variables descriptive statistics will be similar as for continuous variables.

All efficacy, exploratory and safety variables as well as PK plasma concentrations will be summarized by treatment group and at each visit as appropriate using descriptive statistics as above. For continuous variables, descriptive statistics will be summarized both for the observed values and the absolute changes from baseline.

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

Decimal points will be presented as follow:

- If the original variable has 1 or less significant decimal points then Mean, Median, first quartile (Q1), third quartile (Q3), GeoMean, LSmean, CI of the LSmean will be rounded to one more decimal point than the original variable significant decimal points
- If the original variable has 2 or more significant decimal points then Mean, Median, first quartile (Q1), third quartile (Q3), GeoMean, LSmean, CI of the LSmean will be rounded to same decimal points than the original variable significant decimal points
- If the original variable has zero significant decimal points then the SD, SE will be rounded to one more decimal point than the mean
- If the original variable has one or more significant decimal points then the SD, SE will be rounded to the same decimal point than the mean
- Minimum, Maximum: same decimal points as the original variable significant decimal points
- %CV: two decimal points
- Percentage: one decimal point
- Ratio: two decimal points
- CI of the ratio: two decimal points
- N, n: Integer
- P-value: three decimal points (displayed as "<0.001" for p-values lower than 0.001)

For efficacy and exploratory variables, the following statistical models will be used:

Mixed Model Repeated Measures (MMRM)

Mixed Model Repeated Measures (MMRM) analysis using all available data.

Fixed factors of the model will be:

- treatment
- visit
- treatment*visit interaction

The covariates (considered also as fixed) will be:

- type of MI
- baseline value

Visit within subject will be considered as repeated measurements.

The model will use the SP (POW) structure for unequally spaced data variance-covariance matrix as default. Comparisons of AZD5718 [redacted] versus placebo and AZD5718 [redacted] versus placebo will be assessed within the same model.

The reportable results for Normal variables will be:

- Descriptive statistics of the change from baseline calculated as Visit value minus Baseline value for each group;
- The LSmeans and standard errors for each group;
- The difference between active groups and placebo (LSmeans) together with the CI of the difference
- P-value

The reportable results for log-Normal variables will be:

- Descriptive statistics of the change from baseline calculated as EXP[LN(Visit value) - LN(Baseline value)], for each group
- Back transformed LS means (which correspond to the estimated ratio between visit and baseline) for each group
- The ratio between active groups and placebo together with the CI of the ratio;
- P-value

The ratio will be calculated as the exponent of the difference in LS means of the logarithmic transformation; the CI for the ratio will be calculated as the exponent of the CI of the difference of the logarithmic transformation. In case the model will not converge for any reasons, the following back-up solutions will be adopted sequentially:

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

ANCOVA

ANCOVA model using data from Visits 2 and 4.

Fixed factor of the model will be:

- treatment

The covariates (considered also as fixed) will be:

- type of MI
- baseline value

Comparisons of AZD5718 [redacted] versus placebo and AZD5718 [redacted] versus placebo will be assessed within the same model.

The reportable results for Normal variables will be:

- Descriptive statistics of the change from baseline calculated as Visit value minus Baseline value for each group
- The LSmeans and standard errors for each group
- The difference between active groups and placebo (LSmeans) together with the CI of the difference
- P-value

The reportable results for log-Normal variables will be:

- Descriptive statistics of the change from baseline calculated as EXP[LN(Visit value) - LN(Baseline value)], for each group
- Back transformed LS means (which correspond to the estimated ratio between visit and baseline) for each group
- The ratio between active groups and placebo together with the CI of the ratio
- P-value

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

7.2 Adjustments for Covariates

For efficacy and exploratory variables adjustment for the respective baseline value and type of MI (STEMI or NSTEMI as collected in the IRT data base) will be performed.

In case there are at least 5% discrepancies for the type of MI between eCRF and IWRS data, a sensitivity analysis will be performed to assess the primary efficacy endpoint, the first secondary efficacy endpoint, the second secondary efficacy endpoint and the third secondary efficacy endpoint. The sensitivity analysis will consist in running the model using the covariate coming from the eCRF instead of IWRS.

7.3 Handling of Dropouts or Missing Data

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

Partial and completely missing dates will be imputed for study drug first dose date and study drug last dose date. Partial missing dates will be imputed for AE onset date/date becomes serious and AE/Concomitant Medication stop date. Missing start dates for concomitant medications will not be imputed. Imputation rules are described below:

Imputation of Study Drug First Dose:

First dose date and time are mandatory fields. No Imputations are expected.

In the rare cases of missing date, the first dose date of study drug will be imputed if all the following criteria are met:

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

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

Imputation of Study Drug Last Dose:

Last dose date and time are mandatory fields. No Imputations are expected.

In the rare cases of missing date, the last dose date of study drug will be imputed if all the following criteria are met:

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

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

Imputation of AE Onset Date and AE becomes serious date:

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

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

end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

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

With regard to the AE becomes serious date, if after applying all these rules the imputed AE becomes serious date is missing or before the AE start date, then the imputed AE becomes serious date will be the same as the AE start date.

Of note that missing start dates for concomitant medications will not be imputed.

Imputation of AE / Concomitant Medication Stop Date:

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

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

If the AE/CM is ongoing, the stop date will remain as missing. After applying these rules, if the imputed AE or CM stop date is after the date of death, the imputed stop date will be the same as the date of death. Except for the above and unless otherwise specified, complete missing data will not be imputed.

7.4 Interim Analyses

Further details on the conduct of the interim analysis will be delineated in section 8.10.

7.5 Multi-centre Studies and Pooling of Centres

This study will be a multi-centre study conducted at approximately 10 centres in 3 countries. Approximately one hundred and thirty-eight (138 patients with coronary artery disease (CAD) will be randomized to ensure at least 66 evaluable patients receiving 12 weeks treatment with AZD5718 [redacted] or placebo.

Given the low number of countries involved in the study (3 in total, Sweden, Denmark and Finland), the unbalance in terms of number of expected randomized subjects per country and the nature of the primary efficacy variable (a quantitative laboratory result, which is expected to be homogenous across countries) randomization was not stratified by country. For the same reason, country will not be included in the statistical model for assessing the efficacy objectives. The same rationale stands for not pooling centres.

7.6 Multiple Comparisons/Multiplicity

Alpha spending function

The study is composed by 4 main endpoints:

1. primary endpoint: Change in u-LTE_4 at 4 weeks,
2. first secondary endpoint: Change in u-LTE_4 at 12 weeks,
3. second secondary endpoint: Change in CFVR at 12 weeks,
4. third secondary endpoint: Change in CFVR at 4 weeks.

To preserve the overall type1-error at 5% when testing the four endpoints a Hierarchical Procedures will be used (Dmitrienko A. et al 2006). This procedure implies that one will test the four endpoints in a predefined sequence: test of primary endpoint, test of first secondary endpoint, test of second secondary endpoint, test of third secondary endpoint. The test procedure will stop as soon as the first none-significant test, one-sided test at a 5% level, occur and all following test will be declared as non-significant.

Multiplicity test adjustment

All the efficacy and exploratory variables will be assessed for the comparisons of:

5. AZD5718 [redacted] versus placebo,
6. AZD5718 [redacted] versus placebo.

AZD5718 [redacted] comparison versus placebo being included for supporting dose selection in future studies only, meaning that, for all the efficacy and exploratory variables, no adjustment for multiplicity (two groups) is needed.

7.7 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8 Active-Control Studies Intended to Show Equivalence

Not applicable.

7.9 Examination of Subgroups

Type of MI (STEMI or NSTEMI) is used as a stratification factor in the randomization and will be summarized using descriptive statistics.

Two cohorts of patients will be distinguished:

- Cohort 4w treatment: patients randomized before the CSP v3 implementation, who belong to 4 weeks of treatment
- Cohort 12w treatment: patients randomized after the CSP v3 implementation, who belong to 12 weeks of treatment

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Unless otherwise specified, the statistical outputs will be presented jointly for the two cohorts.

8. STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The following summaries will be provided:

- Subject disposition - Cohort 4w treatment and Cohort 12w treatment
- Analysis sets (Efficacy Analysis Set and Safety Analysis Set).
- Subject recruitment by region, country and centre for the Efficacy Analysis Set
- Stratification factors by type of MI (STEMI or NSTEMI) - Cohort 4w treatment and Cohort 12w treatment - as collected in the IRT for the Efficacy Analysis Set.

The following listings will also be provided:

- A listing of all enrolled subjects who discontinued the study or the treatment.
- A listing of all subjects excluded from the Efficacy Analysis set for all randomized subjects.

The randomization scheme together with the various batches of IP will be listed for all subjects randomized.

8.2 Protocol Deviations

The list of IPDs is provided in the AZ ECD Non-compliance Handling Plan (NHP), version 1.0 or higher. Important protocol deviations (IPDs) will be classified as per AZ ECD Non-compliance Handling Plan. Classified IPDs will be assessed for the Efficacy Analysis Set. The number and percentage of subjects with at least one IPD will be summarized globally and for each category, by treatment group and total.

All subjects reporting IPD will be also listed individually, for all randomized subjects.

8.3 Analysis Populations

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

8.3.1 Efficacy Analysis Set

The Efficacy Analysis Set for efficacy will be analysed using the intention to treat (ITT) population. This is in accordance to the ICH E9 guideline suggesting that the analysis of the primary endpoint should be analysed according to the treatment to which subjects were actually randomized. The ITT population will include all patients who were randomized, received at least one dose of study medication and have at least one baseline or postbaseline measurement (primary, secondary and exploratory measurements).

8.3.2 Safety Analysis Set

The Safety Analysis Set will include all subjects who were randomized and received at least one dose of study medication. Subjects will be analysed according to the treatment which they actually received. If a subject received IP from the wrong kit for only a part of the treatment duration and then switched to another, the associated treatment group for that subject will be the treatment group that subject was randomized to. Any important deviations from randomized treatment will be listed and considered when interpreting the safety data. Important deviations are defined in section 8.2. The Safety Analysis Set will be used in both demographic (if appropriate) and safety analyses.

8.3.3 Intent-to-Treat (ITT) Population

Not applicable.

8.3.4 Per Protocol (PP) Population

Not applicable.

8.3.5 Pharmacokinetics (PK) population

The PK analysis set will consist of all subjects in the Efficacy Analysis Set who have received at least one dose of AZD5718, and who have at least one PK sample post dose.

A patient will be considered as having at least one PK sample post dose if he has at least one plasma concentration that is not below LoQ after the first dose.

Subjects will be analysed according to the treatment which they actually received. However, only samples taken on patients planned to receive AZD5718 are analysed. Thus, patients planned to receive placebo but who finally received AZD5718 will not have any result available.

8.4 Demographic and Other Baseline Characteristics

All demographics and baseline characteristics will be presented by treatment group and overall. They will be based on the Efficacy Analysis Set. Demographic and other baseline characteristics are described in section 6.3.

Demographic characteristics and Subject characteristics

Demographic characteristics will be presented by cohort of patients and will include Age (years), Age group (<50; >=50 -<65; >=65 years), sex, race, ethnicity and country. Subject characteristics will include height (cm), weight (kg), weight group (<70; >=70- <=90; >90 kg), BMI ((kg/m2) and BMI group (Normal <25; Overweight >=25-<=30; Obese >30 kg/m2). All these variables will be summarized as described in section 7.1.

Age, sex, race, weight, height and BMI will also be listed for all randomized subjects.

Nicotine and alcohol usage

Nicotine use and alcohol use and consumption will be summarized with descriptive statistics. Alcohol use will be also listed for all randomized subjects.

Medical history

Relevant medical and surgical history and Specific medical and surgical history will be coded in MedDRA 20.0 or higher and will be summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of subjects with any Relevant and Specific medical and surgical history will be summarized by SOC and PT.

8.5 Prior and Concomitant Medications

The WHO-DDE + HD Drug Dictionary version 2017Jun B3 or higher will be used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Medication will be classified as either prior or concomitant (but not both) according to its stop date. Prior medication is defined as any medication with a stop date prior to the first dose of study drug (exclusive).

Concomitant medication is defined as any medication with a start date on or before the last dose of study drug and a stop date on or after the first dose of study drug, or any medication taken prior to last dose of study drug and that is ongoing.

It is of note that classification is not based on eCRF question "Taken prior to study?" but derived according to the medication stop date rule as above.

The imputation method described in section 7.3 will be used in case of medication stop date partially missing. Completely missing start or stop dates will not be replaced, and medication will be classified as concomitant.

The number and percentage of subjects with at least one allowed concomitant medication and the number and percentage of subjects by ATC codes will be provided using the Efficacy Analysis Set. An exhaustive list of disallowed medications (coding and indication wherever applicable) is reported in the Integrated Data Review Plan (IDRP), "Prohibited Medication" tab. Prohibited Medications taken during the study, will be confirmed and flagged by AZ study physician in accordance with CSP v3 section 7.7.

The number and percentage of subjects with any allowed concomitant medication will also be summarized by ATC level 4 (therapeutic subgroup) and product name.

A listing of previous and concomitant medications with ATC codes will be provided for all randomized subjects. Duration (day) will be calculated as stop date minus start date +1. If start date or stop date is partially or completely missing duration will be missing.

8.6 Analysis of Efficacy Parameters

Efficacy parameters include:

- Creatinine-normalised u-LTE_4
- CFVR
- LAD resting mean diastolic flow velocity
- LAD hyperaemic flow velocity
- LV ejection fraction (LVEF) at rest
- LV Global Longitudinal Strain (GLS) at rest and at hyperaemia
- LV Global Circumferential Strain (GCS) at rest
- LV longitudinal early diastolic strain rate

Efficacy endpoints of the study are:

Primary endpoint:

- percent change in creatinine normalized u-LTE_4 at 4 weeks (Visit 4)

Secondary endpoints:

- percent change in creatinine normalized u-LTE_4 at 12 weeks (Visit 4c)
- change in CFVR at 12 weeks (Visit 4c)
- change in CFVR at 4 weeks (Visit 4)

Other secondary endpoints:

- change in LAD resting mean diastolic flow velocity, LAD hyperaemic flow velocity, LV ejection fraction (LVEF) at rest, LV Global Longitudinal Strain (GLS) at rest and at hyperaemia, LV Global Circumferential Strain (GCS) at rest and LV longitudinal early diastolic strain rate at 4 weeks (Visit 4)

To preserve the overall type1-error at 5% when testing these four endpoints a Hierarchical Procedures will be used. This procedure implies that one will test the four endpoints in a predefined sequence: test of main endpoint, test of first secondary endpoint, test of second secondary endpoint, test of third secondary endpoint. The test procedure will stop as soon as the first none-significant test, one-sided test at a 5% level, occur and all following test will be declared as none-significant.

Detailed description of the statistical analyses for each endpoint is reported in the following sections.

In addition to the analyses described below, an overview table for the primary and secondary efficacy results will be provided.

8.6.1 Analysis of primary efficacy variable

The primary efficacy endpoint is to test the null hypothesis that subjects given AZD5718 [redacted] have less than 80% inhibition of creatinine-normalized u-LTE_4 at visit 4 compared to placebo.

The first secondary efficacy endpoint is to test the null hypothesis that subjects given AZD5718 [redacted] have less than 80% inhibition of creatinine-normalized u-LTE_4 at visit 4c compared to placebo.

All the analyses will be performed based on the Efficacy Analysis Set. All the assessments related to the first variable are described in section 6.4.1.

For both the endpoints, the change in creatinine-normalized u-LTE_4 will be analysed using the Mixed Model Repeated Measures (MMRM) described in section 7.1 using data from visit 2, 3, 4 and 4c.

Creatinine-normalized u-LTE_4 is log-Normal distributed. The analysed change from Baseline is calculated as Visit value in log minus the Baseline value in log.

One-sided test will be used to compare the change from baseline observed in the active group, vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05. The reportable results will be those for log-Normal variables.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the statistical model please refer to the Appendix 2 and to the table in Appendix 3.

Back-up solution for statistical model:

In case the model will not converge for any reasons, the following back-up solutions will be adopted sequentially:

- The compound symmetry will be used instead of the SP (POW);
- The primary efficacy variable will be analysed using the ANCOVA model described in section 7.1 for log-Normal variables instead of using the MRMM model.

In addition to the results above, the following will also be generated:

- Descriptive statistics by group for all visits, for the actual value and for the change from baseline. Change from baseline is calculated as Visit value minus Baseline value;
- Graphical representations of change from baseline (mean(SD)) over time and by groups;
- Forest plots based on the results of the two models.

Creatinine-normalized u-LTE_4 will be also listed for Efficacy Analysis Set at each visit.

A sensitivity analysis may be performed as detailed in section 7.2.

8.6.2 Analysis of secondary efficacy variables

Change from baseline in CFVR

The second secondary efficacy endpoint is the change from baseline in CFVR at Visit 4c.

The null hypothesis of no increase in CFVR in subjects given AZD5718 [redacted] compared to placebo will be tested.

The third secondary efficacy endpoint is the change from baseline in CFVR at Visit 4.

The null hypothesis of no increase in CFVR in subjects given AZD5718 [redacted] compared to placebo will be tested.

All the analyses will be performed based on the Efficacy Analysis Set. All the assessments related to the secondary variables are described in section 6.4.2.

Both the second and third secondary endpoints will be analysed using the Mixed Model Repeated Measures (MMRM) described in section 7.1 using data from visit 2, 4 and 4c.

CFVR is log-Normal distributed. The analysed change from Baseline is calculated as Visit value in log minus the Baseline value in log.

One-sided test will be used to compare the change from baseline observed in the active group, vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05. The reportable results will be those for log-Normal variables.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the statistical model please refer to the Appendix 2 and to the table in Appendix 3.

In addition to the results above, the following will also be generated:

- Descriptive statistics by group for all visits, for the actual value and for the change from baseline. Change from baseline is calculated as Visit value minus Baseline value;
- Graphical representations of change from baseline (mean(SD)) over time and by groups;
- Forest plots based on the results of the two models.

CFVR will be also listed for Efficacy Analysis Set at each visit.

A sensitivity analysis may be performed as detailed in section 7.2.

Other secondary variables

The other secondary endpoints related to all other secondary variables are the changes from baseline at Visit 4. The exploratory endpoints related to all other secondary variables are the changes from baseline at Visit 4c.

The other secondary variables are:

- LAD resting mean diastolic flow velocity
- LAD hyperaemic flow velocity
- LV ejection fraction (LVEF) at rest
- LV Global Longitudinal Strain (GLS) at rest and at hyperaemia
- LV Global Circumferential Strain (GCS) at rest
- LV longitudinal early diastolic strain rate

All the analyses will be performed based on the Efficacy Analysis Set. All the assessments related to the secondary variables are described in section 6.4.2.

These variables will be firstly tested for Normality (Normality will be evaluated using Q-Q plots). Then the changes at visit 4 (secondary endpoints) and the changes at visit 4c (exploratory endpoints) will be analysed using Mixed Model Repeated Measures (MMRM) described in section 7.1 using data from visit 2, 4 and 4c.

If the distribution appears to be Normal, the analysed change will be the Visit value minus the Baseline value. The reportable results will be those for Normal variables.

If the distribution appears to be log-Normal, the analysed change will be the Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

The null hypothesis of no difference in subjects given AZD5718 [redacted] compared to placebo will be tested.

Two-sided test will be used to compare the change from baseline observed in the active group vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, also the following will be generated:

- Descriptive statistics by group for all visits, for the actual value and for the change from baseline. Change from baseline is calculated as Visit value minus Baseline value;
- Graphical representations of change from baseline (mean(SD)) over time and by groups;
- Forest plots based on the results of the models.

All these secondary variables will be also listed for Efficacy Analysis Set at each visit.

8.6.3 Analysis of Pharmacokinetic Variables

The analysis will be based on the PK analysis set.

Summary statistics will be provided for plasma concentrations of AZD5718 according to the protocol scheduled time. Plasma concentrations will also be displayed overtime by subject. The number of samples below the limit of quantification will be also be summarized.

8.6.4 Subgroup Analyses

Not applicable.

8.7 Analysis of exploratory parameters and cardiovascular biomarkers

The exploratory parameters are:

- Carotid-femoral pulse wave velocity and brachial pulse wave analysis (cfPWV/bPWA):
  - Augmentation index,
  - Carotid-femoral pulse wave velocity,
  - Pulse pressure amplification,
  - Central pulse pressure,
  - Central blood pressure systolic/diastolic,
  - Brachial blood pressure systolic/diastolic
- Clinical Outcome Assessments:
  - SF-36 (physical component summary (PCS), mental component summary (MCS), perceived change in health and each of the 8 health domain scores)
  - EQ-5D overall score
  - Rose Dyspnoea overall score
  - FACIT-Fatigue Prorated score
- GRACE 2.0 score at baseline
- Exploratory cardiovascular biomarker:
  - Total cholesterol
  - Low density lipoprotein cholesterol (LDL-C)
  - High density lipoprotein cholesterol, (HDL-C)
  - Triglycerides
  - hsTnI (high sensitive Troponin I)
  - hsCRP (High-sensitivity C-Reactive Protein)
  - NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)
  - Lp(a)* (Lipoprotein a)
  - ApoA1* (Apolipoprotein A)
  - ApoB*

The exploratory endpoints related to all the exploratory variables (except GRACE score) are the changes from baseline, at Visit 4 and Visit 4c. The exploratory endpoint for GRACE 2.0 score is based only on the value at baseline.

Detailed description of the statistical analyses for each of these variables is reported in the following sections.

8.7.1 Carotid-femoral pulse wave velocity and brachial pulse wave analysis

cfPWV/bPWA variables will be analysed based on the Efficacy Analysis Set. For the cfPWV/bPWA variables assessment please refer to section 6.9.1.

These variables will be firstly tested for Normality (Normality will be evaluated using Q-Q plots) Then the changes at visit 4 and the changes at visit 4c will be analysed using the MMRM model described in section 7.1 using data from visit 2, 4 and 4c.

If the distribution appears to be Normal, the analysed change will be the Visit value minus the Baseline value. The reportable results will be those for Normal variables.

If the distribution appears to be log-Normal, the analysed change will be the Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

Two-sided test will be used to compare the change from baseline observed in the active group vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, also descriptive statistics by group for all visits, for the actual value and for the change from baseline will be reported. Change from baseline is calculated as Visit value minus Baseline value.

cfPWV/bPWA variables will be also listed for Efficacy Analysis Set at each visit.

8.7.2 Clinical Outcome Assessments

PRO questionnaires will be analysed based on the Efficacy Analysis Set using data from Visits 2, 4 and 4c. For the PRO questionnaires assessment please refer to section 6.9.2.

The changes at visit 4 and the changes on visits 4c on PRO questionnaires will be analysed using the MMRM described in section 7.1 using data from visit 2, 4 and 4c.

PRO questionnaires are normal distributed variables. The analysed change will be the Visit value minus the Baseline value.

Two-sided test will be used to compare the change from baseline observed in the treated group vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05. The reportable results will be those for Normal variables.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, also descriptive statistics by group for all visits, for the actual value and for the change from baseline will be reported. Change from baseline is calculated as Visit value minus Baseline value.

PRO questionnaires scores will be also listed for Efficacy Analysis Set at each visit.

8.7.3 GRACE 2.0 score at baseline

GRACE score at baseline will be summarized descriptively. The description will be performed based on the Efficacy Analysis Set.

GRACE score at baseline will be also listed for Efficacy Analysis Set at each visit.

8.7.4 Cardiovascular biomarkers

Cardiovascular biomarkers will be analysed based on the Efficacy Analysis Set. For additional details see section 6.8.

These variables will be firstly tested for Normality (Normality will be evaluated using Q-Q plots) and then changes at visit 4 and 4c analysed using the MMRM model described in section 7.1 using data from visit 2, 3, 4 and 4c.

If the distribution appears to be Normal, the analysed change will be the Visit value minus the Baseline value. The reportable results will be those for Normal variables.

If the distribution appears to be log-Normal, the analysed change will be the Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

Two-sided test will be used to compare the change from baseline observed in the active group vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05.

Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, also descriptive statistics by group for all visits, for the actual value and for the change from baseline will be reported. Change from baseline is calculated as Visit value minus Baseline value.

Cardiovascular parameters will be also listed for Efficacy Analysis Set at each visit.

8.8 Analysis of Safety

8.8.1 Extent of Exposure and Compliance to Study Treatment

Exposure and compliance are calculated as described in section 6.6.1.

Exposure

Exposure (days) and cumulative exposure over time (days) will be summarized by treatment group and by cohort of patients based on the Safety Analysis Set.

Exposure over time in terms of percentage of patients on treatment, will be also graphically shown by treatment group.

Exposure and actual exposure will be listed for Safety Analysis Set.

Compliance

Both, overall compliance and compliance categories will be summarized by treatment group and overall and by cohort of patients, based on the Safety Analysis Set.

Compliance will be listed for Safety Analysis Set.

8.8.2 Adverse Events

AEs will be assigned to the study phases as described in section 6.6.2.

Unless otherwise specified, AEs and SAEs will be summarized using the Safety Analysis Set by treatment group and by cohort of patients. Percentages will be based on the total numbers of subjects in the treatment group.

Subjects with multiple events in the same category will be counted only once in that category. Subjects with events in more than 1 category will be counted once in each of those categories. Unless otherwise specified On-treatment and Off-treatment phases will be reported separately for each summary table.

The following summary tables will be reported:

An overview table for all the AEs.

The number and percentage of subjects with the most common AEs (frequency>3%) for each Preferred Term (PT);

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The number and percentage of subjects with any AEs for each System Organ Class (SOC) and PT;

The number and percentage of subjects with any AEs by maximum intensity for each PT;

The number and percentage of subjects with any AEs by investigator's causality assessment for each PT;

The number and percentage of subjects with AEs with outcome of death for each SOC and PT;

The number and percentage of subjects with AEs with outcome of death and with causality related to study drug for each SOC and PT in the On-treatment phase.

Key subject information for all subjects with AEs with outcome of death (On-treatment and Off-treatment phases together in the same table).

Time from first dose to AE (day) will be calculated as start date of the AE minus date of first dose +1. Time from last dose to death (day) will be calculated as death date minus date of last dose +1. Time from first dose to death (day) will be calculated as death date minus date of first dose +1. Durations will be calculated only for fully completed dates.

The number and percentage of subjects with death.

The number and percentage of subjects with any SAEs for each SOC and PT;

The number and percentage of subjects with any SAEs with causality related to study drug for each SOC and PT in the On-treatment phase.

Key subject information for all subjects with SAEs.

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

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

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

Durations will be calculated only for fully completed dates.

The number and percentage of subjects with AEs leading to treatment discontinuation for each SOC and PT in the On-treatment phase.

The number and percentage of subjects with AEs leading to treatment discontinuation and with causality related to study drug for each SOC and PT in the On-treatment phase.

Key subject information for all subjects with AEs leading to discontinuation.

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

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

Durations will be calculated only for fully completed dates.

The number and percentage of subjects with AEs leading to treatment interruption for each SOC and PT in the On-treatment phase.

The number and percentage of subjects with any non-serious AEs only for those categories which show more that 5% of frequency, globally and for each PT. This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the CSR. It will be delivered at the same time as the CSR outputs.

Listings will also be presented by subject for all AEs using the Safety Analysis Set. Duration (day) will be calculated as stop date minus start date +1. Duration will be calculated only for complete dates. Listing of SAEs will also be presented for enrolled but not randomized subjects and for subjects who were not exposed to treatment.

8.8.3 Clinical Laboratory Evaluations

Clinical laboratory evaluation is performed based on the Safety Analysis Set. The list and the assessment of all Clinical Laboratory variables are reported section 6.6.3.

Laboratory test results for haematology, coagulation and clinical chemistry

Laboratory test results for haematology, coagulation and clinical chemistry will be summarized in AZ preferred units for each treatment group, and for change from baseline at each visit. Change from baseline to each post-baseline visit will be calculated as the post-baseline visit value minus the baseline visit value.

Classification of the laboratory values with respect to the normal reference range will be provided (low/normal/high). Shifts from baseline to maximum/minimum value during On-treatment phase of this classification will be presented for each treatment group and by cohort of patients.

Hy's law criteria will also be summarized in a double-entry table by cohort of patients.

Laboratory test results for urinalysis

Laboratory test results for quantitative variables (i.e. creatinine and albumin) will be summarized in AZ preferred units for each treatment group, and for change from baseline at each visit. Change from baseline to each post-baseline visit will be calculated as the post-baseline visit value minus the baseline visit value.

Shifts from baseline to maximum value during On-treatment phase will be presented for semi-quantitative variables (i.e. albumin, protein, blood, glucose and Leukocytes). All laboratory data for haematology, coagulation, clinical chemistry and urinalysis will be also presented in listings.

8.8.4 Other Observations Related to Safety

Vital Signs

Vital signs [pulse, pulse oximetry, systolic and diastolic blood pressure] will be summarized for each treatment group, and for change from baseline at each visit based on the Safety Analysis Set. Change from baseline to each post-baseline visit will be calculated as the post-baseline visit value minus the baseline visit value.

The list and the assessment of all Vital Signs variables are reported section 6.6.4.

Vital signs will be also presented in listings including flags for values outside of the reference ranges. Reference ranges are:

- Systolic Blood Pressure: 80-180 mmHg;
- Diastolic Blood Pressure: 50-120 mmHg;
- Pulse: 50-95 beats/min;
- Pulse oximetry: 90-100%.

Also, vital signs associated to CFVR are listed but not used for any statistical analysis.

Electrocardiogram

ECG summaries will be based on the Safety Analysis Set. ECGs details are provided in section 6.6.4. Shifts from baseline to last On-treatment observation will be presented for overall ECG result by cohort of patients. Abnormal 12-lead ECG findings will be presented in listings.

Physical Findings

The list and the assessment of all Physical findings are reported in section 6.6.4. Physical examination results will be collected as:

- normal,
- abnormal but non-clinically significant,
- abnormal clinically significant.

Summary will be based on the Safety Analysis Set.

Body Weight and BMI

Body weight and BMI details are provided in section 6.6.4. Body weight and BMI will be summarized using the Safety Analysis Set.

8.9 Pharmacodynamics

Not applicable.

8.10 Interim analysis

Two administrative interim analyses will be conducted. The first one is planned after at least 45 patients have performed their CFVR measurement at Visit 4 and the second after at least 100 patients have performed their CFVR measurement at Visit 4. The variables for the analyses will be:

- CFVR
- LV Global Longitudinal Strain (GLS) at rest
- LVEF
- Carotid-femoral pulse wave velocity and brachial pulse wave analysis: Augmentation index, Carotid-femoral pulse wave velocity, Pulse pressure amplification and Central pulse pressure
- Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)

These analyses will not have any impact on the overall type-1 error because no changes will be made to the trial based on the outcome of the analyses. The purpose with the interim analyses is to trigger external activities not connected to the trial. Both interim analyses will be performed by study independent personnel.

An Interim Analysis Charter will define the deliverables and procedures for the provision and communication of the planned interim analyses described in the statistical analysis plan. The maintenance of the blind for the Study Team is also addressed. Further details will be given in the Interim Analysis Charter.

The two interim analyses will be focused on to:

Description of the study population:

- Description and comparison of the active groups and the placebo group
- Estimation of the effect on safety variables

The cut-off date for second IA will be determined by the study team.

8.10.1 Description of study population

In order to characterize the population used for the interim analyses, subject disposition, important protocol deviations and analysis sets will be presented.

Subject disposition

Subject disposition - Cohort 4w treatment and Cohort 12w treatment - and analysis sets will be summarized.

Additionally, for the second IA, the demographic characteristics will be presented by cohort of patients and will include Age (years), Age group (<50; >=50 -<65; >=65 years), sex, race, ethnicity and country.

Important protocol deviations

IPDs are described and classified section 8.2.

Classified IPDs will be assessed for the Efficacy Analysis Set. The number and percentage of subjects with at least one IPD will be summarized globally and for each category, by treatment group and total.

8.10.2 Description and comparison of the active groups and the placebo group

First IA

The comparison will be performed on change from baseline at Visit 4 in

- CFVR
- LV Global Longitudinal Strain (GLS) at rest
- LVEF
- Carotid-femoral pulse wave velocity and brachial pulse wave analysis: Augmentation index, Carotid-femoral pulse wave velocity, Pulse pressure amplification and Central pulse pressure
- Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)

The comparison will be based on the Efficacy Analysis Set.

For additional details on these variables see sections 6.4.2, 6.9.1 and 6.8.

The change from baseline for

- CFVR
- LV Global Longitudinal Strain (GLS) at rest
- LVEF
- Carotid-femoral pulse wave velocity and brachial pulse wave analysis: Augmentation index, Carotid-femoral pulse wave velocity, Pulse pressure amplification and Central pulse pressure

will be analysed using the ANCOVA model described in section 7.1 with data from visit 2, and 4.

The change from baseline for

- Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide))

will be analysed using the MMRM model described in section 7.1 with data from visit 2, 3 and 4.

CFVR is log-Normal distributed. The analysed change from Baseline is calculated as Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

All the other variables will be firstly tested for Normality (Normality will be evaluated using Q-Q plots). If the distribution appears to be Normal, the analysed change will be the Visit value minus the Baseline value. The reportable results will be those for Normal variables. If the distribution appears to be log-Normal, the analysed change will be the Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

Two-sided test will be used to compare the change from baseline observed in the active group, vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05. Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, also descriptive statistics will be reported by group for the actual value and for the change from baseline; descriptive statistics will be reported for all visits up to visit 4.

Second IA

The comparison will be performed on change from baseline at Visit 4 and Visit 4c in

- CFVR
- LAD hyperaemic flow velocity
- LV Global Longitudinal Strain (GLS) at rest
- LVEF
- Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)

The comparison will be based on the Efficacy Analysis Set.

For additional details on these variables see sections 6.4.2, 6.9.1 and 6.8.

The change from baseline for

- CFVR
- LAD hyperaemic flow velocity
- LV Global Longitudinal Strain (GLS) at rest
- LVEF

will be analysed using the MMRM model described in section 7.1 with data from visit 2, 4 and 4c for both comparisons (Visit 4 and Visit 4c).

The change from baseline for

- Cardiovascular Biomarkers: hsCRP (High-sensitivity C-Reactive Protein), NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide))

will be analysed using the MMRM model described in section 7.1 with data from visit 2, 3, 4 and 4c for both comparisons (Visit 4 and Visit 4c).

CFVR is log-Normal distributed. The analysed change from Baseline is calculated as Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

All the other variables will be firstly tested for Normality (Normality will be evaluated using Q-Q plots). If the distribution appears to be Normal, the analysed change will be the Visit value minus the Baseline value. The reportable results will be those for Normal variables. If the distribution appears to be log-Normal, the analysed change will be the Visit value in log minus the Baseline value in log. The reportable results will be those for log-Normal variables.

Two-sided test will be used to compare the change from baseline observed in the active group, vs the change from baseline observed in the placebo group. Alpha level will be set at 0.05. Comparison of AZD5718 [redacted] versus placebo will also be assessed within the same model.

For further details on the model please refer to Appendix 2 and to the table in Appendix 3.

In addition to the results above, the following will be reported:

- Descriptive statistics by group for the actual value and for the change from baseline; descriptive statistics for all visits up to visit 4c;
- Graphical representations of change from baseline (mean(SD)) over time and by groups;
- Forest plots based on the results of the two models.

8.10.3 Estimate the effect on safety variables

The effect on safety variables will be presented using the Safety Analysis Set by treatment group. Below a detailed description of the summaries that will be used for the purpose:

Adverse Events

AEs will be assigned to the study phases as described in section 6.6.2.

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Unless otherwise specified, AEs and SAEs will be summarized using the Safety Analysis Set by treatment group and by cohort of patients. Percentages will be based on the total numbers of subjects in the treatment group.

Subjects with multiple events in the same category will be counted only once in that category. Subjects with events in more than 1 category will be counted once in each of those categories.

Only On-treatment phase up to visit 4 at the first IA and up to the cut-off date at the second IA will be reported for each summary table.

The following summary tables will be reported:

An overview table for all the AEs, only for the On-treatment phase.

The number and percentage of subjects with any AEs for each SOC and PT, only for the On-treatment phase.

The number and percentage of subjects with any SAEs for each for each SOC and PT, only for the On-treatment phase.

The following table will be reported for the first IA only:

The number and percentage of subjects with any non-serious AEs only for the On-treatment phase and only for those categories which show more that 5% of frequency, globally and for each PT.

Additionally, for the second IA, the following summary tables will be reported:

The number and percentage of subjects with AEs with outcome of death for each SOC and PT, only for the On-treatment phase.

The number and percentage of subjects with AEs leading to treatment discontinuation for each SOC and PT in the On-treatment phase.

The following listings will be reported for the second IA:

Listings will also be presented by subject for all AEs using the Safety Analysis Set.

Listing of SAEs will also be presented for enrolled but not randomized subjects and for subjects who were not exposed to treatment.

Laboratory test results for haematology, coagulation and clinical chemistry

Clinical laboratory evaluation is performed based on the Safety Analysis Set. The list and the assessment of all Clinical Laboratory variables are reported section 6.6.3.

Laboratory test results for haematology, coagulation and clinical chemistry will be summarized in AZ preferred units for each treatment group, and for change from baseline at each visit up to visit 4 at the first IA and up to visit 4c at the second IA.

Additionally, for the second IA the following tables will be produced:

Classification of the laboratory values with respect to the normal reference range will be provided (low/normal/high). Shifts from baseline to maximum/minimum value during On-treatment phase of this classification will be presented for each treatment group and by cohort of patients.

Hy's law criteria will also be summarized in a double-entry table by cohort of patients.

Laboratory test results for urinalysis

Laboratory test results for quantitative variables (i.e. creatinine and albumin) will be summarized in AZ preferred units for each treatment group, and for change from baseline at each visit. Change from baseline to each post-baseline visit will be calculated as the post-baseline visit value minus the baseline visit value. Only data up to visit 4 at the first IA and up to visit 4c at the second IA will be presented.

Shifts from baseline to maximum value during On-treatment phase will be presented for semi-quantitative urinalysis variables (i.e. albumin, protein, blood, glucose and Leukocytes). Only On-treatment phase up to visit 4 at the first IA and up to visit 4c at the second IA will be used for each summary table.

All laboratory data for urinalysis will be also presented in listing.

9. COMPUTER SOFTWARE

All analyses will be performed by [redacted] using Version 9.1.3 or later of SAS® software. All summary tables and data listings will be prepared utilising SAS® software.

SF-36 scoring will be performed by [redacted] using PRO CoRE Software 1.5.

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

10. REFERENCES

Wiens BL and Dmitrienko A. The Fallback Procedure for evaluating a single family of hypotheses. J Biopharm Stat 2005;15(6):929-42

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

11. APPENDICES

Appendix 1 Variable definitions

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

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

Age group will be displayed for the following 4 categories: <50; >=50 -<65; >=65 years.

Body mass index (BMI; kg/m2) is calculated as: weight (kg) / [height (m)]^2, rounded to two decimal places.

BMI group will be displayed for the following 3 categories: Normal <25; Overweight >=25-<=30; Obese >30 kg/m2.

Weight will be displayed in kilograms (kg), and height will be displayed in centimetres (cm).

Weight group will be displayed for the following 4 categories: <70; >=70- <=90; >90 kg.

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Appendix 2 Statistical analysis and programming details

Mixed Model with Repeated Measures (MMRM) – primary and first secondary endpoints (change at visit 4 and 4c on Creatinine normalized uLTE4):

The SAS code used to implement this test will be similar to that shown below:

PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=REML;
CLASS Trt Mi Subject visit;
MODEL Ch=Trt visit trt*visit MI Base / SOLUTION ddfm=KR;
REPEATED Visit / TYPE=SP(POW)(awtarget) SUB=Subject;
LSMESTIMATE trt*visit 'change at week X - AZD5718 [redacted] vs placebo' 0 -1 0 0 1 0 / **lower** cl testvalue= -1.609437912 /* corresponding to ln(0.2) */;
RUN;

Where awtarget is the expected day of visit.

Mixed Model with Repeated Measures (MMRM) – second and third secondary endpoints (change at visit 4 and 4c on CFVR):

The SAS code used to implement this test will be similar to that shown below:

PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=REML;
CLASS Trt Mi Subject visit;
MODEL Ch=Trt visit trt*visit MI Base / SOLUTION ddfm=KR;
REPEATED Visit / TYPE=SP(POW)(awtarget) SUB=Subject;
LSMESTIMATE trt*visit 'change at week X - AZD5718 [redacted] vs placebo' -1 0 1 0/ **upper** cl;
RUN;

Where awtarget is the expected day of visit.

Mixed Model with Repeated Measures (MMRM) – change at visit 4 and 4c on Other secondary variables, all exploratory variables and cardiovascular biomarkers:

The SAS code used to implement this test will be similar to that shown below:

PROC MIXED data=dataset COVTEST NOCLPRINT METHOD=REML;
CLASS Trt Mi Subject visit;
MODEL Ch=Trt visit trt*visit MI Baseline / SOLUTION ddfm=KR;
REPEATED Visit / TYPE=SP(POW)(awtarget) SUB=Subject;
LSMESTIMATE trt*visit ' change at week 4c - AZD5718 [redacted] vs placebo' -1 0 1 0 / cl ;
RUN;

Where awtarget is the expected day of visit.

ANCOVA model – change at visit 4 on all variables except cardiovascular biomarkers at first Interim analysis:

The SAS code used to implement this test will be similar to that shown below:

```
PROC MIXED data=dataset;
CLASS Trt MI;
MODEL Ch= Trt MI Base;
LSMESTIMATE trt ' change at week 4 – AZD5718 [redacted]mg vs Placebo'   -1  1 /  cl ;
RUN;
```

NB: LSMESTIMATE statement must be adapted based on data used in the model.

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Appendix 3 Summary table of statistical models

ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
Primary endpoint:						
Change of Creatinine-normalised u-LTE$_4$ at visit 4	4	2(B), 3,4, 4c	MMRM	Lower one-sided test of difference	0.05	Log-Normal
Secondary endpoint:						
First secondary endpoint						
Change of Creatinine-normalised u-LTE$_4$ at visit 4c	4c	2(B), 3,4, 4c	MMRM	Lower one-sided test of difference	0.05	Log-Normal
Second secondary endpoint						
Change of CFVR at visit 4c	4c	2(B), 4, 4c	MMRM	Upper one-sided test of difference	0.05	Log-Normal
Third secondary endpoint						
Change of CFVR at visit 4	4	2(B), 4, 4c	MMRM	Upper one-sided test of difference	0.05	Log-Normal
All other secondary endpoints						
Change in: • LAD resting mean diastolic flow velocity • LAD hyperaemic flow velocity • LV ejection fraction (LVEF) at rest • LV Global Longitudinal Strain (GLS) at rest and at hyperaemia • LV Global Circumferential Strain (GCS) at rest • LV longitudinal early diastolic strain rate	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

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ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
Exploratory endpoints:						
Change in: • LAD resting mean diastolic flow velocity • LAD hyperaemic flow velocity • LV ejection fraction (LVEF) at rest • LV Global Longitudinal Strain (GLS) at rest and at hyperaemia • LV Global Circumferential Strain (GCS) at rest • LV longitudinal early diastolic strain rate	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change in Carotid-femoral pulse wave velocity and brachial pulse wave analysis (cfPWV/bPWA): • Augmentation index, • Carotid-femoral pulse wave velocity, • Pulse pressure amplification, • Central pulse pressure, • Central blood pressure systolic/diastolic, • Brachial blood pressure systolic/diastolic	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change in Carotid-femoral pulse wave velocity and brachial pulse wave analysis (cfPWV/bPWA): • Augmentation index, • Carotid-femoral pulse wave velocity, • Pulse pressure amplification,	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

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ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
• Central pulse pressure, • Central blood pressure systolic/diastolic, • Brachial blood pressure systolic/diastolic						
Change in Clinical Outcome Assessments: • SF-36 • EQ-5D • Rose Dyspnoea score • FACIT-Fatigue	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal
Change in Clinical Outcome Assessments: • SF-36 • EQ-5D • Rose Dyspnoea score • FACIT-Fatigue	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal

Exploratory cardiovascular biomarker:

Change in: • Total cholesterol • Low density lipoprotein cholesterol (LDL-C) • High density lipoprotein cholesterol, (HDL-C) • Triglycerides • hsTnI (high sensitive Troponin I) • hsCRP (High-sensitivity C-Reactive Protein) • NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide) • Lp(a) (Lipoprotein a) • ApoA1 (Apolipoprotein A) • ApoB	4	2(B), 3, 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

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ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
Change in: • Total cholesterol • Low density lipoprotein cholesterol (LDL-C) • High density lipoprotein cholesterol, (HDL-C) • Triglycerides • hsTnI (high sensitive Troponin I) • hsCRP (High-sensitivity C-Reactive Protein) • NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide) • Lp(a) (Lipoprotein a) • ApoA1 (Apolipoprotein A) • ApoB	4c	2(B), 3, 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
First Interim analysis						
Change of CFVR at visit 4	4	2(B), 4	ANCOVA	Two-sided test of difference	0.05	Log-Normal
Change of LV-GLS at rest at visit 4	4	2(B), 4	ANCOVA	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change of LVEF at rest at visit 4	4	2(B), 4	ANCOVA	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change in Carotid-femoral pulse wave velocity and brachial pulse wave analysis (cfPWV/bPWA): • Augmentation index, • Carotid-femoral pulse	4	2(B), 4	ANCOVA	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

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ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
wave velocity, • Pulse pressure amplification, • Central pulse pressure						
Change in Cardiovascular biomarkers: • hsCRP (High-sensitivity C-Reactive Protein) • NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)	4	2(B), 3, 4	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Second Interim analysis						
Change of CFVR at visit 4	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Log-Normal
Change of CFVR at visit 4c	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Log-Normal
Change of LAD hyperaemic flow velocity at visit 4	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change of LAD hyperaemic flow velocity at visit 4c	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change of LV-GLS at rest at visit 4	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change of LV-GLS at rest at visit 4c	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
CIL Project Number:	40343		

ENDPOINT	Visit tested	Data used	STATISTICAL MODEL	TEST	ALPHA LEVEL	VARIABLE TRANSFORMATION
Change of LVEF at rest at visit 4	4	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change of LVEF at rest at visit 4c	4c	2(B), 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change in Cardiovascular biomarkers: • hsCRP (High-sensitivity C-Reactive Protein) • NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)	4	2(B), 3, 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.
Change in Cardiovascular biomarkers: • hsCRP (High-sensitivity C-Reactive Protein) • NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)	4c	2(B), 3, 4, 4c	MMRM	Two-sided test of difference	0.05	Normal / Log-Normal depending on Q-Q plots.

12. TABLE SHELLS AND SPECIFICATIONS

14. SUMMARY TABLES AND FIGURES, LISTINGS, AND NARRATIVES

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Table 14.1.7 - Subject characteristics - Cohort 12 weeks treatment (Efficacy Analysis Set)

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Table 14.1.13 - Stratification factors recorded at randomization by IRT - Cohort 4 weeks treatment and Cohort 12 weeks treatment (Efficacy Analysis Set)

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Figure 14.2.1.2 - Analysis of Change from baseline in Creatinine-normalised u-LTE_4, MMRM at Week 4 and Week 12 - Forest plot (Efficacy Analysis Set)

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Figure 14.2.1.3 - Change from baseline in CFVR by Visit, mean(SD) (Efficacy Analysis Set)

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Table 14.2.1.7 - Analysis of Change from baseline in CFVR at Week 12, MMRM (Efficacy Analysis Set)

Table 14.2.1.7.1 - Analysis of Change from baseline in CFVR at Week 12, sensitivity analysis, MMRM (Efficacy Analysis Set) (optional)

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Table 14.2.1.11 - Change from baseline in LAD hyperaemic flow velocity by Visit, summary statistics (Efficacy Analysis Set)

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Table 14.3.2.10 - Adverse events, by preferred term and investigator's causality assessment - Cohort 12 weeks treatment - On treatment (Safety Analysis Set)

Table 14.3.2.11 - Adverse events, by preferred term and investigator's causality assessment - Cohort 4 weeks treatment - Off treatment (Safety Analysis Set)

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NA

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Appendix 16.1 Study Information

Appendix 16.1.6 - Patients receiving the various batches of investigational products (All randomized subjects)

Appendix 16.1.7 - Randomization scheme and codes (All randomized subjects)

Appendix 16.2 Subject Data Listings

16.2.1 Disposition of each subject (completion/discontinuation)

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D7550C00003
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Appendix 16.2.1.1 - Discontinued subjects (All enrolled subjects)

16.2.2 Protocol deviations

Appendix 16.2.2.1 - Subjects with important protocol deviations (All randomized subjects)

16.2.3 Subjects and data excluded from efficacy analysis

Appendix 16.2.3.1 - Subjects excluded from the Safety and the Efficacy Analysis Set (All randomized subjects)

16.2.4 Demographic and baseline characteristic

Appendix 16.2.4.1 - Demographic and baseline characteristics (All randomized subjects)

Appendix 16.2.4.2 - Alcohol use (All randomized subjects)

Appendix 16.2.4.3 – Prior and concomitant medication (All randomized subjects)

16.2.5 Treatment compliance (and/or drug concentration data)

Appendix 16.2.5.1 - Administration of investigational product (Safety Analysis Set)

16.2.6 Individual efficacy and pharmacokinetic response data

Appendix 16.2.6.1 - Efficacy assessments (Efficacy Analysis Set)

16.2.7 Adverse event listing, by subject

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Appendix 16.2.7.2 - Serious adverse events (Enrolled but not randomised subjects and for subjects who were not exposed to treatment)

16.2.8 Listing of individual laboratory measurements, by subject

Appendix 16.2.8.1 - Laboratory safety variables (Safety Analysis Set)

16.2.9 Listing of vital signs

Appendix 16.2.9.1 - Individual vital signs data (Safety Analysis Set)

16.2.10 Listing of other safety data

Appendix 16.2.10.1 - Abnormalities in electrocardiogram (Safety Analysis Set)

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