STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca AB	Protocol/CIP Number:	D9150C00003
CIL Project Number:	40597		

Protocol/CIP No. D9150C00003

A randomised, double-blind, placebo-controlled, multi-centre, sequential design, phase IIa study to evaluate safety and tolerability of epicardial injections of AZD8601 during coronary artery bypass grafting surgery

Statistical Analysis Plan

Prepared for:
AstraZeneca AB

Final Version 3.0 Date 19JUL2021

[redacted]

VERSION HISTORY OF IMPLEMENTED PLANS

Version	Date	Revision Author	Comments
1.0	10APR2019	[redacted]	NA
2.0	15MAY2020	[redacted]	Updated according to Clinical Study Protocol v5.0; Kit listing information added; NYHA graphic removed; "Chiltern" changed to "Covance"
3.0	19JUL2021	[redacted]	"Covance" changed to "Labcorp Drug Development" Only [redacted] dose will be used due to study termination; Added COVID 19 related outputs;

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			Section 12 removed as of being included in shells; Visit timepoints revisited to be more precise; Section 4.6 added: study terminated and high dose cohort will not be represented. Analysis for stress echo removed as of having lack of data. Defenitions and analysis for d6MWT and MCWS removed as of being optional data and not being collected. Visit windows updated to be include larger interval of data FSH, LH removed from Table 9 as of being collected for inclusion criteria only. Added details for method of echocardiogram used for analysis. Author of the document updated. Added some units and updated for consistency.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

15O PET	O-15 Radiowater Positron Emission Tomography
ACS	Abnormal Clinically Significant
ACS	Acute Coronary Syndrome
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANCS	Abnormal Not Clinically Significant
APTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AZ	AstraZeneca
AZRand	Parexel Randomisation Solution for AstraZeneca
BILI	Total Bilirubin
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CFVhy	CFVR During Adenosine Infusion Induced Hyperaemia
CFVR	Coronary Flow Velocity Reserve
CFVratio	The Ratio Between Resting and Maximal Possible Coronary Blood Flow in the Coronary Flow Reserve
CFVrest	CFVR in Rest Condition
CI	Confidence Interval
CM	Concomitant Medication
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CS	Compound-symmetry Structure
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
d6MWT	Digital 6-min Walk Test
dECG	Digital Electrocardiogram
DMG	Data Monitoring Group
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End of Treatment
FSH	Follicle-stimulating Hormone
GeoMean	Geometric Mean
GeoCV	Geometric Coefficient of variation
Hb	Hemoglobin
HCT	Haematocrit
[redacted]	High-sensitive Troponin T

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IDRP	Integrated Data Review Plan
ICF	Informed Consent Form
INR	International Normalized Ratio
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAD	Left Anterior Descending artery
LCA	Left Coronary Artery
LCX	Left Circumflex
LH	Luteinizing Hormone
LS	Least Squares
LSmean	Least Square Mean
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVEDV	Left Ventricular End Diastolic Volume
LVESV	Left Ventricular End Systolic Volume
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MCWS	Maximum Continuously Walked Steps
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
modRNA	Modified Messenger Ribonucleic Acid
MoP	Manual of Procedures
MPR	Myocardial Perfusion Reserve
[redacted]	N-terminal pro b-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Pharmacodynamics
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PRO	Patient Reported Outcomes
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQ	Seattle Angina Questionnaire
SD	Standard Deviation
SE	Standard Error
SI	System International
sMBF	Stress Myocardial Blood Flow
SOC	System Organ Class
SOP	Standard Operating Procedures
SP (POW)	Spatial Power Covariance Structures
SQRT	Square Root
SRB	Safety Review Board
SRC	Safety Review Committee

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ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGF-A	Vascular Endothelial Growth Factor A
VEGF121	VEGF containing 121 Amino Acids
VEGF165	VEGF containing 165 Amino Acids
WBC	White Blood Cell
WHO	World Health Organisation

2. INTRODUCTION

Coronary artery disease (CAD) is characterized by obstructive atherosclerotic lesions in the arterial wall resulting in limitation in myocardial blood flow, eventually leading to ischemia and ventricular dysfunction. Besides the apparent acute coronary syndrome (ACS) and myocardial infarction, CAD is the primary single cause of left ventricular (LV) systolic dysfunction leading to heart failure. Overall, CAD and heart failure are closely linked and left ventricular function serves as an important determinant of prognosis and can be used to predict disease outcome.

Coronary revascularization in many instances can relieve symptoms, improve prognosis and left ventricular function and is therefore applicable therapy not only in ACS but in symptomatic stable CAD. However, in spite of medical advancements in treatment of especially ischemic heart failure there is a clear unmet medical need in addressing the medical therapies for this patient population.

Therapeutic vascular growth is emerging as a concept for management of vascular indications. The vascular endothelial growth factor (VEGF) is a protein coded by a 7-exon gene localized on chromosome 6 and serves as a major angiogen in normal cardiac development. The VEGF gene is normally spliced into 4 different forms; of these, VEGF121 (containing 121 amino acids) and VEGF165 (165 amino acids) appear to be the most important.

The VEGF family members are key regulators of vascular growth and the VEGF-A member, and especially its [redacted] administered as recombinant protein or via naked or adenoviral vector-mediated gene transfer has received much attention for its potential beneficial effects in cardiovascular medicine. However, randomised controlled trials have not lived up to expectations and evidence of clinical efficacy is inconclusive.

The overall reason(s) for the lack of consistency and conclusive clinical benefit is currently somewhat unclear but may include factors such as suboptimal pharmacokinetics (PK) and local concentrations of the protein, poor gene transfer efficiency, inappropriate dosing and regression of immature vessels, prolonged expression of the paracrine factor as well as growth factor-related adverse effects such as oedema and hypotension. To circumvent the issues associated with recombinant protein and gene transfer modalities, synthetic and chemically modified messenger ribonucleic acid (modRNA) has been put forward as a non-immunogenic and non-integrating modality for efficient and transient expression of target proteins in mammalian cells.

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AZD8601 is [redacted] under development as a novel modality for local production of human VEGF-A protein and is developed for the treatment of ischemic heart disease.

This statistical analysis plan (SAP) is based on the final clinical study protocol (CSP) version 5.0 dated 27Feb2020. The SAP includes detailed procedures for executing the statistical analysis related to the safety and explorative objectives of the study, with the exception of:

- The exploration of the relationship between the digital 6-min walk test (d6MWT) and maximum continuously walked steps (MCWS); and echocardiographic or other parameters;
- The potential exploratory determination of plasma concentrations of [redacted] (AZD8601);
- The potential exploration of anti-drug immunogenicity,

which will be described in separate documents.

In addition, the process for conducting the interim analyses for the safety reviews will be developed in separate charters.

The SAP is finalized and signed prior to database hard lock, to avoid any potential bias. If needed, revisions to the approved SAP may be made prior to database hard lock in a SAP amendment.

3. STUDY OBJECTIVES

The primary objective of this study is:

- To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery with moderately impaired systolic function.

Secondary objectives: none.

Safety objectives: Not applicable due to safety being Primary objective.

The explorative objectives of this study are:

- To assess the effect of AZD8601 in patients undergoing CABG surgery on regional and global stress myocardial blood flow (sMBF) measured with O-15 radiowater positron emission tomography (15O PET) imaging;
- To assess the effect of AZD8601 in patients undergoing CABG surgery on regional and global quantitative myocardial perfusion reserve (MPR) measured with 15O PET;
- To assess the effect of AZD8601 on left ventricular end-diastolic and end-systolic volumes (Left ventricular end diastolic volume (LVEDV), Left ventricular end systolic

volume (LVESV)) and global left ventricular ejection fraction (LVEF) by echocardiography;
- To assess the effect of AZD8601 on regional myocardial wall motion measured by echocardiography and strain analysis in patients undergoing CABG surgery;
- To assess the effect of AZD8601 on stress cardiac function induced by adenosine measured by echocardiography, optionally Coronary Flow Velocity Reserve (CFVR) in the Left Anterior Descending (LAD) artery;
- To assess the effect of AZD8601 on clinical symptoms in terms of New York Heart Association (NYHA) class, Seattle Angina Questionnaire (SAQ) and Kansas City Cardiomyopathy Questionnaire (KCCQ);
- To assess change from baseline in terms of [redacted] related to AZD8601 treatment;
- To determine the VEGF-A protein concentration in plasma in patients undergoing CABG surgery, after epicardial injections of AZD8601 or placebo;
- To collect samples for exploratory research aimed at investigating biomarkers including but not limited to VEGF-A downstream biomarkers involved in PK, pharmacodynamics (PD), efficacy, safety and tolerability related to AZD8601 treatment;
- To collect and store samples for future potential exploratory determination of plasma concentrations of [redacted](AZD8601) after epicardial injections of AZD8601;
- To collect and store samples for potential exploration of anti-drug immunogenicity;
- Optional: To assess the effect of AZD8601 on change in d6MWT and MCWS parameter and to explore the relationship between these and echocardiographic or other parameters collected here in CAD patients (Not applicable in Germany).

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 randomised, double-blind, placebo-controlled, sequential design, multicenter study in patients with moderately impaired systolic function undergoing CABG surgery. The study will be a multi-center study conducted at approximately 4 sites initially in 1 country, but with the possibility to expand to further countries if needed.

Patients suitable for the study will be identified by screening of hospital medical records of patients scheduled for elective CABG surgery with an expected waiting time to surgery less than 3 months but more than 2 weeks. If a patient is found potentially suitable, he/she will be asked about participation in this study and invited to a screening/enrolment visit (Visit 1). Before any study related procedures are conducted, the patient will receive information about the study and will be asked to sign Informed Consent Form (ICF). The patients will then undergo baseline assessments (Visit 1 and Visit 2).

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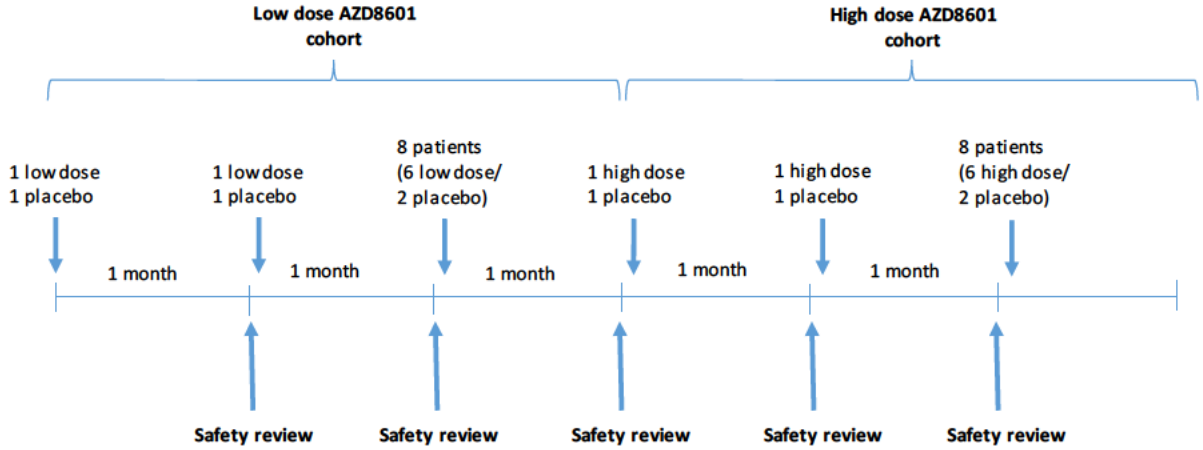
To achieve 7 evaluable patients in each treatment group, low dose [redacted] high dose [redacted] and placebo, 21 in total – 24 patients will initially be randomised. An evaluable patient is defined as a patient who completed the study. See Section 5.1 for further details.

The study will include two cohorts of 12 patients each, which will receive either a low or high dose of AZD8601 in a sequential, dose ascending fashion. Within each cohort 8 patients will be randomised to receive AZD8601 and 4 patients to placebo. Each cohort will be divided into 3 sentinel dosing cohorts. See Figure 1. The first and second sentinel cohorts will include 2 patients each – 1 patient randomised to placebo and 1 to AZD8601. The third sentinel cohort will include the 8 remaining patients on that dose level: 2 placebo, 6 AZD8601. After each sentinel cohort, before proceeding dosing the next, safety data from up to 1 month post dose (Visit 5) from the current cohort and the available data from previous cohorts, will be reviewed. The same applies before continuing to the high dose cohort. The procedure will be repeated in the same way within the high dose cohort. Two parallel safety reviews will be done:

- Blinded safety review board (SRB) consisting of study investigators and AZ personnel;
- Study independent unblinded safety review committee (SRC) consisting of a combination of internal AstraZeneca (AZ) expertise and external experts.

In addition, to the existing blinded and unblinded safety review after each sentinel cohort, an additional unblinded Data Monitoring Group (DMG) will perform data review on emerging safety and clinical data. This DMG will consist of internal AstraZeneca employees independent of the study team.

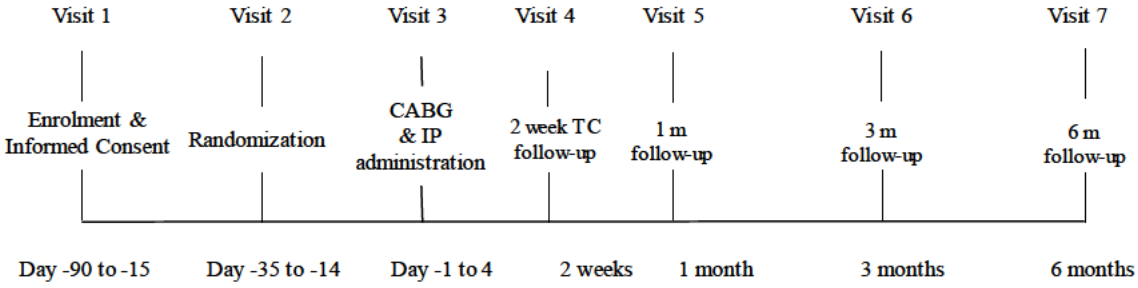
Figure 1: Outline of sentinel dosing cohorts



Patients will be followed up at 2 weeks, 1 month, 3 months, and 6 months post CABG surgery. The Study flow chart is presented in

Figure *2* below. For details and timings of the study assessments refer to Table 2 and Table 3 in Section 6.

Figure 2: Study flow chart



4.2 Discussion of Study Design

This study is a randomised, double-blind, placebo-controlled, multicenter, sequential design study to assess the safety and tolerability of AZD8601 versus placebo. Placebo has been chosen as the comparator to assess safety and tolerability of both injection procedure and AZD8601. Parameters for potential efficacy will be addressed under explorative endpoints.

The study examines the effects of AZD8601 given as epicardial injections in patients with stable CAD with decreased LVEF going through elective CABG. Primarily the safety and tolerability of AZD8601 in increasing doses in patients going through CABG will be assessed. In addition, exploratory objectives that address the capabilities of AZD8601 to improve global and local myocardial perfusion and/or left ventricle function in the studied patient population will be explored.

There will be three treatment arms. Patients will be randomised to placebo, low dose AZD8601 or high dose AZD8601 in the proportion [redacted] In a sequential dose ascending fashion, the first cohort will receive either placebo or low dose AZD8601 and the second cohort will receive either placebo or high dose AZD8601. Within each dose cohort 8 patients will be randomised to AZD8601 and 4 to placebo.

The investigational product (IP) will be given as epicardial injections into the accessible ischemic border zone according to a tailor-made individualized injection map (please see further details in the protocol). The low dose of AZD8601 will consist of [redacted] per injection site. The high dose of AZD8601 will consist of [redacted] per injection site.

This study will assess ascending total doses of [redacted] (low dose) and [redacted] (high dose) to determine clinical tolerability and safety. The dose will be administered with approximately [redacted] inter-site distance with [redacted] epicardial injections per patient, with [redacted] per injection.

The high dose and the low dose will be administered with a high and a low concentration of the drug substance respectively, keeping injection volume constant and number of injections per cm of border zone similar between the dose groups. [redacted] Thus dose increment per injection site as well as total dose will not exceed 10-fold from the starting dose. Patients receiving placebo will be dosed according to the same rationale but will receive vehicle injections, i.e [redacted]

4.3 Method of Assignment of Subjects to Treatment Groups

Upon completion of the randomisation requirements specification, the randomisation will be produced by Parexel using the Parexel randomisation solution for AstraZeneca (AZRand). The study will include two dose cohorts which will receive a low or high dose of AZD8601. Dosing for each dose cohort will proceed in three sentinel cohorts. In the first and second sentinel cohorts 2 patients will be randomised to placebo or AZD8601 at a ratio of [redacted]. In the third sentinel cohort, 8 patients will be randomised to placebo or AZD8601 at a ratio of [redacted].

For each sentinel cohort an additional set of random numbers will be generated according to the same treatment allocation ratio. The replacement patient will receive the lowest available randomisation code having the same treatment allocation.

AZ Supply Chain will assign randomisation codes.

4.4 Blinding

The study will have a double-blind design. Placebo solution for injection will match appearance of AZD8601 solution for injection.

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 randomisation scheme during the conduct of the study, with the following exceptions:

- AZRand generating the randomisation scheme;
- AstraZeneca Supply Chain;
- The AstraZeneca or CRO personnel carrying out the labelling and packaging of patient specific treatments;
- The pharmacy personnel preparing study drug at the site;
- The SRC performing safety evaluation before proceeding with dosing the next sentinel cohort and before dose escalation.
- The DMG consisting of internal AstraZeneca employees independent of the study team as outlined in the combined SRC and DMG charter, who are reviewing unblinded emerging safety data and clinical data for clinical program development

This documentation will be kept in a secure location until the end of the study.

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the site Investigator(s) or pharmacists. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient 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 investigational product 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 patient have been made and documented.

4.5 Determination of Sample Size

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. The sample size is based on experience from previous studies to obtain adequate safety, tolerability and technical feasibility data to achieve the objectives of the study while exposing as few patients as possible to study procedures.

It is estimated that 24 patients (8 per arm) need to be randomised and receive treatment in order to achieve 21 evaluable patients (7 per arm).

Accounting for replacement patients, it is estimated that up to approximately 33 patients may be randomised.

4.6 Changes according to study termination

Due to low recruiting rate the study is prematurely terminated after 11 subjects have already been recruited. Therefore, no subjects were assigned to the second sentinel cohort – high dose [redacted]. Consequently, no analysis and no comparisons will be provided for high dose cohort.

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

5.1 Changes in the Conduct of the Study

NA

5.2 Changes from the Analyses Planned in the Protocol/CIP

- CSP Section 8.4.1 includes use of concomitant medication, and LVEF as safety assessments. However, these are not described in CSP Section 5.2 Safety assessments.

It is clarified in the SAP that LVEF is considered and evaluated as exploratory assessment and concomitant medications as subject characteristics;

- CSP synopsis stated that geometric mean and geometric SD are used for log-Normal exploratory variables. Geometric coefficient of variation will be used instead of geometric SD

6. BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

The subject assessments to be conducted at each scheduled visit are displayed in Table 2 and Table 3.

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Table 2: Schedule of Assessments: enrolment and treatment periods

	Screening/ Enrolment	Randomisation	CABG surgery & IP administration					Notes
Visit	**Visit 1**	**Visit 2**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Informed consent	x							
Inclusion/exclusion criteria	x	x						
Demographic data	x							
Medical History	x	x	x					
Concomitant medication	x	x	x	x	x	x	x	Incl. herbal/ nutritional supplements
Serology	x							
Nicotine use	x							Previous and current
Height	x							
Weight and BMI	x							
FSH and LH sampling	x							Females only
Randomisation		x						After the pre-operative cardio thoracic surgery conference
IP administration				x				

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	Screening/ Enrolment	**Randomisation**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**	**Visit 2**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Safety and tolerability:								
Adverse event review	x (SAE only)	x (SAE only)	x (SAE only)	x	x	x	x	
Blood pressure and pulse	x	x		x	x	x	x	Supine. V3: 4 times/day on Day 1-3 and at discharge on Day 4 Day 1: one assessment done pre-surgery and three post-surgery.
Pulse oximetry (saturation)				x	x	x	x	V3: 4 times/day on Day 1-4 Day 1, one assessment done pre-surgery and three post-surgery.
Digital Electrocardiogram (dECG) with digital source file	x	x	x	x	x	x	x	V3: Once Day -1 as baseline, 2 times/day on Day 1-4 Day 1 both timepoints will be post-surgery.
Telemetry			x	→				Start on Day -1, pause during CABG, re-start post-surgery and continue until discharge

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	Screening/ Enrolment	**Randomisation**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**	**Visit 2**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Physical examination	x (brief)	x		x				
Blood and urine samples for safety laboratory evaluations	x		x				x (at discharge)	
Hemopericardium and/or tamponade assessment with echocardiography							x	
Exploratory Assessments								
Filming/photo of injection procedure				x				
15O PET (sMBF)		x						At visit 2, PET can be done on a separate day if more feasible
CT angiography		x						
Echocardiography	x							
Stress echocardiography (with LAD CFVR)	x							
Optional. AZ activity app: d6MWT, MCWS (N/A Germany)		x						Timepoint of supervised d6MWT to be noted in electronic case report form (eCRF)

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	Screening/ Enrolment	**Randomisation**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**	**Visit 2**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
KCCQ	x							
Seattle Angina Questionnaire	x							
NYHA classification	x							
Exploratory Biomarkers								
Blood sampling for [redacted]	x	x	x	x	x	x	x	At V2: Only collected if time between V1 and V2 is > 2 weeks At V3: Pre-surgery, Day -1. Post-surgery 3, 6, 24, 34, 48 and 72 h after first epicardial injection (2).
Plasma samples for VEGF-A protein analysis to be stored in biobank		x	x	x	x	x	x	V2: 2 samples with at least 15 min in between. V3: Pre-surgery, Day -1. Post-surgery 3, 6, 24, 34, 48 and 72 h after first epicardial injection (2).
Plasma samples for future exploratory analysis of AZD8601 [redacted] to be stored in biobank			x	x		x		Pre-surgery, Day -1. Post-surgery 1, 3 and 48 h after first epicardial injection (2).

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	Screening/ Enrolment	**Randomisation**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**	**Visit 2**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Plasma samples to be stored in biobank for potential exploration of anti-drug immunogenicity		x						
Plasma samples to be stored in biobank for potential exploratory analyses	x			x		x	x	V3: 6, 48 and 72 hours after first epicardial injection (2).

1) Visit 1 and Visit 2 can be combined, however PET and CFVR assessments should be done on separate days
2) Post- surgery samples should be taken as close to the specified timepoint as possible, but a time window of ± 1 hour is allowed.

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Table 3: Schedule of assessments: Follow-up period

	Follow-up				**Notes**
Visit	**Visit 4 (TC)**	**Visit 5**	**Visit 6**	**Visit 7**	
Day/month (time window)	**14 (±2 days)**	**1 month (±3 days)**	**3 months (±14 days)**	**6 months (±14 days)**	
Concomitant medication		x	x	x	Including herbal/ nutritional supplements
Safety and tolerability:					
Adverse event review	x	x	x	x	
Blood pressure and pulse		x	x	x	Supine
dECG with digital source file		x	x	x	
Physical examination		x	x (brief)	x (brief)	
Blood and urine samples for safety laboratory evaluations		x	x	x	
Exploratory Assessments					
15O PET (sMBF)		x	x		
CT angiography			x		
Echocardiography		x	x	x	
Stress echocardiography (with LAD CFVR)				x	
Optional. AZ activity app: d6MWT, MCWS (N/A Germany)		x	x	x	Timepoint of supervised d6MWT to be noted in eCRF.

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	Follow-up				**Notes**
Visit	**Visit 4 (TC)**	**Visit 5**	**Visit 6**	**Visit 7**	
Day/month (time window)	**14 (±2 days)**	**1 month (±3 days)**	**3 months (±14 days)**	**6 months (±14 days)**	
KCCQ		x	x	x	
Seattle Angina Questionnaire		x	x	x	
NYHA classification		x	x	x	
Exploratory Biomarkers					
Blood sampling for [redacted]		x	x	x	
Plasma samples for VEGF-A protein analysis		x			
Plasma samples to be stored in biobank for potential exploration of anti-drug immunogenicity		x	x	x	
Plasma samples to be stored in biobank for potential exploratory analyses		x	x	x	

Order of assessments: not all assessments are applicable for all visits, but this is the order when they are done:

1. PRO (KCCQ, SAQ) and NYHA classification
2. Supervised d6MWT
3. ECG, AE-review, physical examination, vital signs (blood pressure, pulse, pulse oximetry)
4. Safety laboratory sampling, samples for VEGF, for AZD8601, for hsTnT and NT-proBNP, for anti-drug immunogenicity and for biobanking
5. Echo, CFVR
6. 15O PET/CT angiogram
7. Post-surgery blood samples

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7.4.1 Screening/Enrolment period

Pre-study screening:

Patients suitable for the study will be identified by screening of hospital medical records of patients scheduled for elective CABG surgery with an expected waiting time to surgery less than 3 months but more than 2 weeks. If found potentially suitable based on the inclusion and exclusion criteria for the study, the patient will be invited to a screening visit (Visit 1). The patient will be asked to come fasting on Visit 1.

Visit 1 – Screening, enrolment and baseline assessments (Day -90 to -15):

Patients will be asked to sign ICF and will undergo baseline assessments of echocardiography parameters including stress cardiac function measurement.

KCCQ, SAQ and NYHA class will be used for assessment of clinical symptoms.

Visit 2 – Randomisation and baseline assessments (Day -35 to -14):

This visit includes two parts: the patient visit to site and a cardio thoracic surgery conference.

Visit 2 may take place close in time to Visit 1, optimally latest 14 days before planned CABG surgery. It is also possible to combine Visit 1 and Visit 2 however PET and CFVR assessments should be (must) done on separate days. All other assessments can be performed on any of these two days.

Please note: the timeframe between PET assessment and the date of planned CABG ideally should be 14 days to secure pre-operative conference, randomisation procedure, order and delivery of investigational product. However, this timeframe can be reduced if the above mentioned activities can be accommodated within a shorter period of time.

Patients who fulfil all the inclusion criteria and none of the exclusion criteria will be randomised at this visit. The patient will be fasting on arrival to the clinic.

Baseline assessments of rest and sMBF by 15O PET will be done. Patients will undergo a 15O PET and contrast-enhanced computed tomography (CT) scan to generate a combined CT-angiogram and cardiac perfusion map.

Patients will be invited to participate in the optional AZ Activity App component of the study. The App will be activated on-site at visit 2 and a supervised d6MWT will take place (N/A in Germany).

Randomisation will take place after the outcome of the pre-operative cardio thoracic surgery conference is available. This should optimally occur latest Day -10, however, this timeframe

can be reduced if delivery of investigational product to the site can be warranted before the planned date of CABG.

Further assessments during Visit 2 are outlined in Table 2.

Pre-operative cardio thoracic surgery conference to decide individual injection map.

Based on quantitative coronary angiogram and positron emission tomography (PET)/CT perfusion map available from Visit 2, consensus will be reached regarding surgical procedure individualized for each patient. A tailor-made injection map of approximately 1 cm inter-site distance with 30 epicardial injections will be determined to guide the injection procedure during CABG to target the ischemic but viable (rest perfusion > 60% of normal myocardium resting flow of 1 mL/g/min) myocardium.

Treatment will be focused on the left coronary artery (LCA) territory, starting with the largest ischemic area, i.e. either left anterior descending LAD or left circumflex (LCX) supply territory. If the number of injections remaining after complete treatment of the first largest ischemic area is not enough to treat the second one as identified by the injection map, the area will be partially treated applying the same injection distance.

The individualized injection map will be determined by an expert committee of study site staff involved in the study. Prior to the meeting, the interpretation of the PET scan will be agreed with the core lab responsible person.

If identified that the patient, according to the PET scan, has a too small ischemic area to accommodate the intended 30 injections the patient will not be randomised or receive IP.

7.4.1 Treatment period

Visit 3 – CABG surgery and IP administration (Day -1 to 4):

At Visit 3, the patient will come to the clinic and undergo assessments as outlined in Table 2.

During the operation, following by-pass grafting immediately before reperfusion, patients will receive 30 epicardial injections of the treatment they have been randomised to: placebo or AZD8601. Further details will be provided in a separate manual of procedures (MoP).

Patients will be required to remain hospitalized at the study site hospital approximately 4 days post-surgery for safety and tolerability evaluation with extensive monitoring in line with normal clinical routine. Significant pericardial effusion will be excluded by assessment of hemopericardium and/or tamponade using bed-side echocardiography and assessment of maximum thickness of pericardial fluid before discharge from the hospital.

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7.4.1 Follow-up period

Visit 4 - Telephone contact follow-up (Day 14 ±2 days):

Two weeks after the operation, the investigator or research nurse will make a phone call to the patient to follow-up on adverse events (AEs).

Visit 5 – Follow-up (1 month ±3 days):

The patient will be fasting on arrival to the clinic. During this visit, rest and stress 15O PET perfusion scan will be performed and also echocardiography including assessment of pericardium, regional/global cardiac function and cardiac volumes will be performed. For other assessments, refer to Table 3.

Visit 6 – Follow up (3 months ±14 days):

The patient will be fasting on arrival to the clinic. A CT angiogram will be performed after PET studies. All other assessments will be identical to Visit 5.

Visit 7 – Final follow-up (6 months ±14 days):

The patient will be fasting on arrival to the clinic. Echocardiography, including stress cardiac function, regional/global cardiac function and cardiac volumes will be performed.

For other assessments, refer to Table 3.

6.2 Time Point Algorithms

6.2.1 Relative Day

The date of first dose of study drug 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 Study Drug + 1.

For days before the first dose of study drug:

Date of Assessment – Date of First Dose of Study Drug.

6.2.2 Windows and analysis flag

For the purpose of the statistical analysis, the visit numbers will be recalculated in terms of study days since the first day of the study medication, as illustrated in the following table for all variables except cardiovascular biomarkers, plasma VEGF-A concentrations:

Table 4: Analysis Windows (All variables except cardiovascular biomarkers, plasma VEGF-A concentrations)

Analysis Visit	Visit Window for Analysis (Days)	Scheduled Study Day
Baseline	< 1[a]	NA
Day 1	1[b]	1
Day 2	2	2
Day 3	3	3
Day 4	4	4
Visit 4 (Day 14)	5-21	14
Visit 5 (Day 30)	22-61	30
Visit 6 (Day 91)	62-136	91
Visit 7 (Day 182)	137-197	182

a Includes all measurements collected prior to first dose of study drug intake. If the measurement is collected on the day of first dose of study drug, and the time of collection or the planned timepoint flag cannot determine if the measurement was before or after study drug intake, then it will be considered as collected after study drug intake.

b Includes all measurements collected on the day of first dose of study drug intake, at the time of drug intake and after on Day 1.

Baseline value used for statistical analysis is the last available value (scheduled or unscheduled visit) prior to first dose of study drug. 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 prior to the first day of study drug, or on the first day of study drug prior to study drug intake, the baseline value will be:

- the arithmetic mean for normal distributed variables,
- the geometric mean for log-normal distributed variables,
- the worst case for categorical values.

For example, for ECGs and Physical examinations, if there is a tie in the overall ECG evaluation results at baseline, the baseline value will be the worst clinically significant value.

For all the other visit windows 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 analysed value will be:

- the arithmetic mean for normal distributed variables,
- the geometric mean for log-normal distributed variables,
- the worst case for categorical values.

This rule will apply to all data (including vital signs collected at different planned timepoints on the same study day), except pre- and post-adenosine vital signs associated with CFVR which will be presented only in listings, by pre- and post-adenosine timepoints, cardiovascular biomarkers, plasma VEGF-A concentrations.

Cardiovascular biomarkers

Table 5: Analysis Windows - cardiovascular biomarkers

Analysis Visit (AVISIT)	Time point (ATPTN)	Visit Window for Analysis (Days)	Scheduled Study Day	Scheduled Study Hours
Baseline		< 1[a]	NA	NA
Day 1	3	CRF visit	1	3
Day 1	6	CRF visit	1	6
Day 2	24	CRF visit	2	24
Day 2	34	CRF visit	2	34
Day 3	48	CRF visit	3	48
Day 4	72	CRF visit	4	72
Visit 4 (Day 14)	336	CRF visit	14	336
Visit 5 (Day 30)	720	CRF visit	30	720
Visit 6 (Day 91)	2184	CRF visit	91	2184
Visit 7 (Day 182)	4368	CRF visit	182	4368

a Includes all measurements collected prior to first dose of study drug intake.

Baseline value used for statistical analysis is the last available value (scheduled or unscheduled visit) prior to first dose of study drug. 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. Unless otherwise specified, if several

measurements are collected on the last date prior to the first day of study drug, or on the first day of study drug prior to study drug intake, the baseline value will be the

- the arithmetic mean for normal distributed biomarkers,
- the geometric mean for log-normal distributed biomarkers

For all the other visits the nominal (case report form (CRF)) visits will be used. Measurements collected outside the nominal visits will be labelled as "Unscheduled visit" and will not be used in any statistical analysis but will be listed.

Plasma VEGF-A concentrations

For plasma VEGF-A concentrations, nominal (case report form (CRF)) visits will be used. To be noted that the nominal visit "Day 1 pre-surgery" correspond to the CSP measurements planned at visit 3 day – 1 pre-surgery.

Baseline value will be calculated as the geometric mean of the two measurements at Visit 2. If one measurement is missing, then Visit 2 plasma concentration will be the non-missing measurement. If both measurements are missing, Visit 2 plasma concentrations will be missing.

Plasma VEGF-A concentrations collected at unscheduled visits will be labelled as "Unscheduled visit" and will not be used in any statistical analysis but will be listed.

6.2.3 Phase

For the purpose of statistical analysis, 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 6: Analysis Phase

Phase	Phase Window for Analysis (Days)
Pre-treatment	<1a
On-treatment	1b to ≤ 7 days after last dose of study drug
Follow-up	>7 days after last dose of study drug

[a] Includes all measurements collected prior to first dose of study drug intake. 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.

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

6.3 Baseline Assessments

Baseline values used for statistical analysis are defined in section 6.2.2.

The following will be summarized as baseline assessments prior to initial study drug administration:

- Demographics (age, age group (<50; >=50 -<65; >=65), ethnic group, race, sex, weight (kg), height (cm), body mass index (BMI) (kg/m2), BMI group [normal (<25 kg/m2), overweight (25-30 kg/m2) and obese (>30 kg/m2)], and country.
- Relevant medical and surgical history.

6.4 End of Treatment

Regarding ECG measurements, assessment at end of 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.

6.5 Efficacy Variables

Not Applicable.

6.6 Drug Concentration Measurements and Pharmacokinetic Parameters

Pharmacokinetics for AZD8601 will not be assessed as part of the study. Plasma samples will be collected and stored for potential assessment of plasma AZD8601 levels. Any results will be presented outside of this Clinical Study Report (CSR).

6.7 Safety Assessments

Safety assessments include AEs, vital signs (pulse, pulse oximetry and blood pressure), physical examination, clinical laboratory safety evaluations (haematology, coagulation, clinical chemistry and urinalysis), 12-lead ECG, hemopericardium and/or tamponade assessment and pregnancy.

6.7.1 Extent of Exposure and Compliance to Study Treatment

This study being a single dose administration, extent to exposure and compliance to study treatment will not be considered.

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6.7.2 Adverse Events

Adverse Events will be collected from Visit 3 day 1 (CABG surgery) throughout the treatment period and including the follow-up period (until Visit 7). SAEs will be recorded from the time of informed consent (Visit 1).

AEs will be assigned to Pre-treatment/On-treatment/Follow-up treatment phase based on AE start date and time as follows:

- Pre-treatment phase: The time before first administration of study drug. Note that only SAEs will be assigned to Pre-treatment phase,
- On treatment phase: The time from first administration of study drug until 7 days after last dose of study drug,
- Follow-up phase: More than 7 days after last dose of study drug.

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 Pre-treatment phase,
  - If the AE starts on or after the first dose of IP through 7 days after 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 Follow-up 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 Pre-treatment phase,
  - If the AE starts on or after the date of the first dose of IP through 7 days after last dose day 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 Follow-up treatment phase.

- In addition, if the start date of an AE is completely missing, the AE should be assigned as follow:
  - If the end-date is known and is before the date of first study IP then the AE will be assigned to the Pre-treatment phase,
  - If the end-date is completely missing or if the end-date is on or after the date of first IP no assignation can be done.

Note that if the AE start in the On-treatment phase and became serious in the Follow-up phase the AE will be assigned as Serious to the On- treatment phase.

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.

Missing AE severity will not be replaced.

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

6.7.3 Clinical Laboratory Evaluations

Blood and urine samples for determination of hematology, coagulation, clinical chemistry and urinalysis will be taken at the times indicated in Table 2 and Table 3.

The hematology, coagulation, clinical chemistry and urinalysis will be performed at a local laboratory at or near to the Investigator site. AstraZeneca will provide the same type of urine dipstick test kit to all sites.

The laboratory variables given below will be measured.

Table 7: Standard Clinical Laboratory Evaluation Panels

Hematology/Hemostasis (whole blood)	White blood cell (WBC) count Red blood cell (RBC) count Hemoglobin (Hb) Hematocrit (HCT) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin 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 Alkaline phosphatase (ALP) "LIVER PANEL" Alanine aminotransferase (ALT) "LIVER PANEL" Aspartate aminotransferase (AST) "LIVER PANEL" Total bilirubin "LIVER PANEL" Follicle-stimulating hormone (FSH) (females only, at screening) Luteinizing Hormone (LH) (females only, at screening)
Urinalysis	Glucose (dipstick) Albumin (quantification/semi-quantification) Protein (dipstick) Blood (dipstick) WBC (leukocytes) (dipstick) Creatinine (quantification)

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

The date, time of collection and results (values, local units and local reference ranges) will be recorded on the appropriate eCRF.

Conversions to SI units will be applied where needed using the units and conversion factors as reported in the AZ "Labcodes" Excel file version dated 12 June 2018 or higher.

Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

Unless otherwise specified, laboratory data obtained from Day 1 of study drug up to 7 days after the last dose of study drug will be considered as obtained during the on-treatment phase. Baseline values and visit values are defined as in Section 6.2.2.

Change from baseline to each post-baseline visit for hematology, coagulation and clinical chemistry will be defined as the post-baseline visit value minus the baseline visit value.

Hematology, coagulation and clinical chemistry laboratory values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on local lab units reference range indicator.

Patients with laboratory changes are defined as follows:

- Patients with increase: Patients with baseline laboratory value within normal reference ranges and any post-baseline value > normal reference range higher limit.
- Patients with decrease: Patients with baseline laboratory value within normal reference ranges and any post-baseline value < normal reference range lower limit.
- Patients with Treatment emergent laboratory change: Patients who fulfil either or both the criteria above.

Potential Hy's Law

Potential Hy's low is defined as AST or ALT ≥ 3xULN together with BILI ≥ 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 BILI, but there is no specified timeframe within which the elevations in transaminases and BILI must occur.

If the patient does meet PHL criteria the Investigator will complete the three Liver CRF Modules as information becomes available.

6.7.4 Other Observations Related to Safety

Unless otherwise specified, all safety data displayed below and obtained from Day 1 of study drug up to 7 days after the last dose of study drug will be considered as obtained during the on-treatment phase. Baseline values and visit values are defined as in Section 6.2.2.

Vital Signs

Vital signs will include pulse, pulse oximetry, systolic and diastolic blood pressure. Vital signs will be obtained at time points indicated in Section 6, Table 2 and Table 3 (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. Patients should be in the same position for the vital signs measurements throughout the study.

For the purpose of the analysis, if several measurements are collected on the same study day (including different planned timepoints), the average value will be used for that study day. However, this rule will not apply to pre and post-adenosine vital signs data which will not be averaged.

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

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Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

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

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 180 mmHg
Diastolic blood pressure	50 -120 mmHg
Pulse	50- 95 bpm
Pulse oximetry	90-100 %

Electrocardiogram (ECG) and Telemetry

12-lead ECG recordings will be collected using provided ECG machines according to the assessments schedule presented in Section 6, Table 2 and Table 3. Telemetry online ECG surveillance for rhythm monitoring and arrhythmia detection will be also done at the given time points.

12-lead ECG:

Baseline values are defined as in Section 6.2.2. On Day 1, Visit 3, the two ECG measurements should be done post-surgery with reasonable time interval. The investigator will make an overall evaluation of the ECG as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

Abnormal values shall not be recorded as AEs unless deemed clinically significant.

Physical Examination

A complete physical examination will be performed at Visits 2, 3 and 5 and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

At Visits 1, 6 and 7 a brief physical examination will be performed (general appearance, skin, abdomen and musculoskeletal, cardiovascular and respiratory systems). Baseline values are defined as in Section 6.2.2.

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 or abnormal at each assessment and if abnormal, whether the abnormality is clinically significant or not.

Hemopericardium and/or tamponade assessment with echocardiography

Hemopericardium and/or tamponade will be assessed by clinical routine echocardiography evaluation to assess any postoperative pericardial effusion at Visit 3, day 4 post CABG.

Pregnancy

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur before Visit 3, the patient will be withdrawn from the study and will not receive IP. Should a pregnancy occur after Visit 3, the follow-up assessments will be performed as planned until Visit 7, with the exception of PET and CT which will be omitted due to radiation.

All pregnancies and outcomes of pregnancy should be reported to AZ and registered as IPD, except if the pregnancy is discovered before the study patient has received any study drug and the patient withdrawal from the study and not received IP.

6.8 Pharmacodynamics

Except samples taken for analysis of exploratory biomarkers, no other pharmacodynamics samples will be taken.

6.9 Exploratory Variables

6.9.1 15O PET and CT angiogram

A dynamic oxygen-15 labelled water positron emission tomography (15O PET)/CT scan, generates a combined image of coronary angiogram superimposed on a myocardial perfusion map to locate areas of myocardial ischemia and dysfunction. 15O PET/CT scan will be performed at the times presented in the study assessments schedule, Section 6, Table 2 and Table 3.

The output variables will be the following:

- Regional sMBF in the myocardial region that received injections (mL/g/min) - tMBFs;
- Global sMBF (mL/g/min) - gMBFs;
- Regional MPR in the myocardial region that received injections (ratio) - tCFR;
- Global MPR (ratio) - gCFR.

Change from baseline to each visit will be defined as the visit value minus the baseline value. Baseline value and visit values are defined as in Section 6.2.2.

Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

6.9.2 Echocardiography and Stress Echocardiography (optional LAD CFVR)

Rest Echocardiography

Comprehensive echocardiographic examination will be performed with subjects in the left recumbent position at rest at the times presented in the study assessments schedule, Section 6, Table 2 and Table 3.

The output variables will be:

- Regional wall motion at rest in the LV segments where IP was received (%); measured at baseline (pre CABG), 1, 3 and 6 months post CABG.
- Global longitudinal strain (%) measured at baseline and 1, 3 and 6 months post CABG.
- Cardiac volumes (LVEDV (mL) and LVESV (mL)) and ejection fraction (%) (LVEF) at rest measured at baseline (pre CABG), 1, 3 and 6 months post CABG.

Measurements performed using Biplane Simpson method will be used for analysis. Otherwise, TomTec Triplane method will be used. Other methods will be reported in listings only.

Change from baseline to each visit will be defined as the visit value minus the baseline value. Baseline value and visit values are defined as in Section 6.2.2.

Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

Stress Echocardiography and Optional LAD CVFR

Stress echocardiography with focus on left ventricular function and LAD CFVR will be assessed at rest and during adenosine infusion induced hyperaemia. The CFVR measurement will be included for sites with the ability to perform adenosine assisted CFVR. Assessments will be performed at the times presented in the study assessments schedule, Section 6, Table 2 and Table 3.

The output variables will be:

- Global longitudinal strain at stress (%) and LVEF (%) at stress measured at baseline (pre CABG) and 6 months post CABG.
- CFVR in rest condition (CFVrest) measured at baseline (pre CABG) and 6 months post CABG.
- CFVR During Adenosine Infusion Induced Hyperaemia (CFVhy) measured at baseline (pre CABG) and 6 months post CABG
- Ratio between resting and maximal possible coronary blood flow in the coronary flow reserve (CFVratio) calculated at baseline (pre CABG) and 6 months post CABG.

Only data from poor, acceptable and good images will be used for the analyses. All data (including not valid) will be provided in listing format.

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Change from baseline for Global longitudinal strain at stress (endoGLS) and ejection fraction at stress (LVEF) will be defined as the visit value minus the baseline value. Baseline value and visit values are defined as in Section 6.2.2.

Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

For CFVR assessments, change from baseline to each visit will be defined as the visit value minus the baseline value.

Ratio from endpoint to baseline (%) will be defined as the exponent of the logarithm of the visit value minus the logarithm of the baseline value.

Change from baseline to each post-baseline visit to be used in the statistical model will be defined as the logarithm of the visit value minus the logarithm of the baseline value.

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

6.9.3 Clinical Outcome Assessments

Two Patient Reported Outcomes (PRO) questionnaires will be used to address symptoms and impact of coronary disease: KCCQ and SAQ.

The PRO questionnaires used in this study will all be collected by paper, patient-self completed, and responses should be entered by the Site personnel or designated data management staff in the appropriate sections of the CRF.

The time points for the above listed PRO assessments are given in the schedule of assessments in Section 6, Table 2 and Table 3.

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a sensitive, specific, and responsive health-related quality of life measure for heart failure. It is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.

In the KCCQ, an overall summary score can be derived from the physical function, symptom (frequency and severity), social function and quality of life domains. For each domain, the validity, reproducibility, responsiveness and interpretability have been independently established. Scores are transformed to a range of 0-100, in which higher scores reflect better health status. KCCQ Summary Scores are described in Table 8 below.

Table 8: KCCQ Summary Scores

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

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
5 / Symptom Frequency	Q5=Times Fatigue Limited Ability	All of the time = 1 Several times a day = 2 At least once a day = 3 3 or more times a week but not every day = 4 1-2 times a week = 5 Less than once a week = 6 Never over the past 2 weeks = 7	S7 = [(Q7 response) – 1]/6 S9 = [(Q9 response) – 1]/4 and Symptom Frequency Score is calculated as below: **Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)**
7 / Symptom Frequency	Q7=Times Shortness of Breath Limit Ability	All of the time = 1 Several times a day = 2 At least once a day = 3 3 or more times a week but not every day = 4 1-2 times a week = 5 Less than once a week = 6 Never over the past 2 weeks = 7	
9 / Symptom Frequency	Q9=Times Shortness of Breath Limit Sleep	Every night = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5	

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Question # / Domain	**Detailed Questions**	**Response and associated code response**	**Summary Score algorithm**
4 / Symptom Burden	Q4=Bothered by Swelling in Feet/Ankles/Legs	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5 I've had no swelling/fatigue/shortness of breath = 5	If at least one of questions Q4, Q6 and Q8 is not missing, then Symptom Burden Score is calculated as below: **Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4**
6 / Symptom Burden	Q6=Bothered by Fatigue	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5 I've had no swelling/fatigue/shortness of breath = 5	
8 / Symptom Burden	Q8=Bothered by Shortness of Breath	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5	

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Question # / Domain	Detailed Questions	Response and associated code response	Summary Score algorithm
		I've had no swelling/fatigue/shortness of breath = 5	
			Total Symptom Score = mean of the following available summary scores: **Symptom Frequency Score** **Symptom Burden Score**
10 / Self-Efficacy	Q10=Know What to Do if Heart Failure Gets Worse	Not at all sure = 1 Not very sure = 2 Somewhat sure = 3 Mostly sure = 4 Completely sure = 5	If at least one of Questions 10 and 11 is not missing, then Self-Efficacy Score is calculated as below: **Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4**
11 / Self-Efficacy	Understand Heart Failure Symptoms from Getting Worse	Do not understand at all = 1 Do not understand very well = 2 Somewhat understand = 3 Mostly understand = 4 Completely understand = 5	
12/Quality of Life	Heart Failure Limited Enjoyment of Life	It has extremely limited my enjoyment of life = 1 It has limited my enjoyment of life quite a bit = 2 It has moderately limited my enjoyment of life = 3 It has slightly limited my enjoyment of life = 4	If at least one of Questions 12, 13 and 14 is not missing, then Quality of Life Score is calculated as below:

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

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

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

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

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Only KCCQ overall summary score will be of interest for this study.

Change from baseline to each visit is defined as the visit value minus the baseline value. Baseline value and visit values are defined as in Section 6.2.2.

Seattle Angina Questionnaire

The SAQ is a sensitive, specific, and responsive health-related quality of life instrument for coronary artery disease. It's a self-administered, disease-specific measure for patients with CAD that is valid, reproducible, and sensitive to clinical change.

The SAQ quantifies patients' physical limitations caused by angina, the frequency of and recent changes in their symptoms, their satisfaction with treatment, and the degree to which they perceive their disease to affect their quality of life. Each scale is transformed to a score of 0 to 100, where higher scores indicate better function (e.g., less physical limitation, less angina, and better quality of life).

Table 9: SAQ Summary Scores

Question # / Domain	Detailed Questions	Response and associated numerical code response	Summary Score algorithm
1 / Physical Limitations	Q1a= Dressing Yourself Q1b= Walking Indoors on level ground Q1c= Showering Q1d= Climbing a hill or flight of stairs without stopping Q1e= Gardening, vacuuming, or carrying groceries Q1f= Walking more than a block at a brisk pace Q1g= Running or jogging Q1h= Lifting or moving heavy objects Q1i= Participating in strenuous sports	Extremely Limited=1 Quite a bit Limited=2 Moderately Limited=3 Slightly Limited=4 Not at all Limited=5 Limited for other reasons or did not do the activity=6	If the responses to Questions Q1a through Q1i are not 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 is treated as a missing. Missing values are assigned the average score for that level of activity. Activities are grouped into 3 levels of exertional requirements. The lowest level includes Q1a, Q1b and Q1c; the middle level includes Q1d, Q1e and Q1f; the highest level includes Q1g, Q1h, and Q1i. If any one item in a group is missing, then assign the average value of the other group items to the missing item. If all items in the lowest or the highest level are missing, then assign each item the mean of the items in the middle level. If all items in the middle level are missing, then assign each item the average of the means of the lowest and highest levels. If more than 4 items are missing in this scale then no reasonable score for this dimension can be calculated. After accounting for any missing items the physical limitation score for this dimension is computed by standardizing the mean response of all nine items as follows: **Physical Limitation Score = 100*(mean response – 1)/4**

2 / Angina Stability Scale	Q2= chest pain, tightness or angina when doing more strenuous activities	Much more often = 1 Slightly more often = 2 About the same = 3 Slightly less often = 4 Much less often =5 Had no chest pain over the last 4 weeks= 6	If the response is 6 (no chest pain over the last 4 weeks) then set the response to 3 (about the same). If the response is missing then angina stability cannot be computed and will be missing. Otherwise, the angina stability score is computed by standardizing the results as follows: **Angina Stability Score = 100*(response – 1)/4**
3 / Angina Frequency	Q3= How many times chest pain, tightness or angina	4 or more times per day = 1 1-3 times per day=2 3 or more times per week but not every day=3 1-2 times per week=4 Less than once a week=5 None over the past 4 weeks=6	If at least one question response is present then the angina frequency is computed by standardizing the mean response as follows: **Angina Frequency Score = 100*(response – 1)/5**
	Q4 = How many times nitroglycerin use for chest pain, tightness or angina	4 or more times per day = 1 1-3 times per day=2 3 or more times per week but not every day=3 1-2 times per week=4 Less than once a week=5 None over the past 4 weeks=6	
4 / Treatment Satisfaction	Q5 = Bothersome to take pills for chest pain, tightness or angina	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3	If responses to Q5 to Q8 are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 for Q5 is treated the same as a response of 5 following the clinical logic

		Slightly bothersome = 4 Not bothersome at all = 5 My doctor has not prescribed pills = 5	that having no pills prescribed is equivalent to it being 'not bothersome at all' to take anti-anginal medications. If at least two responses are present then the treatment satisfaction score is computed by calculating the mean response and standardizing the results as follows: **Treatment Satisfaction Score = 100*(response – 1)/4**
	Q6 = Satisfied that everything possible is being done to treat chest pain, tightness or angina	Not satisfied at all = 1 Mostly dissatisfied = 2 Somewhat satisfied = 3 Mostly satisfied = 4 Completely satisfied = 5	
	Q7 = Satisfied with explanations from doctor	Not satisfied at all = 1 Mostly dissatisfied = 2 Somewhat satisfied = 3 Mostly satisfied = 4 Completely satisfied = 5	
	Q8 = Satisfied with the current treatment?	Not satisfied at all = 1 Mostly dissatisfied = 2 Somewhat satisfied = 3 Mostly satisfied = 4 Completely satisfied = 5	
5 / Quality of Life	Q9 = How much chest pain, tightness or angina has limited enjoyment of life?	It has extremely limited my enjoyment of life = 1 It has limited my enjoyment of life quite bit = 2 It has moderately limited my enjoyment of life = 3	If the responses to Q9, Q10 and Q11 are not values 1, 2, 3, 4 or 5 then the response is set to missing. If at least two responses are present then Quality of Life score may be computed by standardizing the mean response as follows:

		It has slightly limited my enjoyment of life = 4 It has not limited my enjoyment of life = 5	**Quality of Life = 100*(response – 1)/4**
	Q10 = Feel for the rest of your life with chest pain, tightness or angina	Not satisfied at all= 1 Mostly dissatisfied=2 Somewhat satisfied=3 Mostly satisfied=4 Completely satisfied=5	
	Q11 = How often think or worry that you may have a heart attack or die suddenly	I can't stop thinking or worrying about it=1 I often think or worry about it=2 I occasionally think or worry about it=3 I rarely think or worry about it=4 I never think or worry about it=5	

For each SAQ summary score (Physical limitation score, Angina stability score, Angina frequency score, Treatment satisfaction score, Quality of life score), change from baseline to each visit is defined as the visit value minus the baseline value. Baseline value and visit values are defined as in Section 6.2.2.

6.9.4 NYHA Classification

Classification of heart failure symptoms will be done according to New York Heart Association (NYHA) at the time points given in Table 2 and Table 3, Section 6.

Patients' heart failure is classified according to the severity of their symptoms using one of four categories based on how much they are limited during physical activity (lower class indicating better symptoms).

Table 10: NYHA classification

Class	Patient Symptoms
I	Without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnea.
II	Slight limitation of physical activity. The patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnea.
III	Marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion.

6.9.5 Digital 6-minute walk test and Maximum continuously walked steps (optional)

No analysis for d6MWT and MCWS is expected as of being optional data and consequently having no data available.

6.9.6 Filming/photo of injection procedure

The injection procedure (approximately 10 minutes) will be filmed and, if possible, high resolution photos taken (or extracted from the film). This will not be used for any analyses or be part of the CSR, it will be done for documentation purpose. This is described in further detail in a MoP.

6.10 Exploratory Biomarkers

Samples for determination of research biomarkers will be taken at the times presented in the study assessments schedule, Section 6, Table 2 and Table 3.

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Below is the list of exploratory biomarkers that will be part of the CSR. Any other exploratory biomarker that will not be part of this CSR is not listed below. Post- surgery samples at Visit 3 should be taken as close to the specified timepoint as possible, but a time window of ± 1 hour is allowed.

Table 11: Exploratory biomarkers

Panel Name	Biomarkers
Cardiovascular Biomarkers*	[redacted]
VEGF-A protein**	[redacted]

*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.

**Samples to be handled by a central laboratory will be collected, labelled stored and shipped as detailed in the Laboratory Manual. Samples from patients treated with either AZD8601 or placebo will be analysed for VEGF-A protein.

Cardiovascular Biomarkers:

The date, time of collection and results (values, local units and local reference ranges) will be recorded on the appropriate eCRF.

Conversions to System International (SI) units will be applied where needed using the units and conversion factors as reported in the AZ "Labcodes" Excel file version dated 12 June 2018 or higher.

Unless otherwise specified, cardiovascular data obtained from Day 1 of study drug up to 7 days after the last dose of study drug will be considered as obtained during the on-treatment phase.

Change from baseline to each visit will be defined as the visit value minus the baseline value. Baseline value and visit values are defined in section 6.2.2.

Ratio from endpoint to baseline (%) will be defined as the exponent of the logarithm of the visit value minus the logarithm of the baseline value.

Change from baseline to each post-baseline visit to be used in the statistical model will be defined as the logarithm of the visit value minus the logarithm of the baseline value.

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Cardiovascular biomarkers will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range).

Value below the lower limit of quantification (LoQ) will be set at LoQ/(sqrt(2)).

Plasma VEGF-A concentrations:

Plasma VEGF-A concentration is potential unblinded parameter. Live data will be provided to the blinded team only after database look.

Value below the lower limit of quantification (LoQ) will be set to missing.

Change from baseline to each visit will be defined as the visit value minus the baseline value. Baseline value and visit values are defined in section 6.2.2.

Ratio from endpoint to baseline (%) will be defined as the exponent of the logarithm of the visit value minus the logarithm of the baseline value.

Change from baseline to each post-baseline visit to be used in the statistical model will be defined as the logarithm of the visit value minus the logarithm of the baseline value.

VEGF-A protein plasma concentration, AUC[0-72]

The area under the concentration-time curve (AUC [0-72]) post dosing (µmol*h/L) will be calculated by linear up/ log down trapezoidal summation.

Linear up/ log down trapezoidal summation is a combination of the linear and logarithmical methods. When concentrations increase over time for a given time interval the linear up trapezoidal method is used. When concentrations decrease over time for a given time interval, the logarithmic down trapezoidal method is used.

Let C1 (µmol/L) be the concentration at t1, C2 (µmol/L) the concentration at t2 and t2 – t1 the duration of the time interval (hours):

The linear up trapezoidal method uses linear interpolation between data points to calculate the AUC. For a given time interval (t2 – t1), the AUC can be calculated as follows:

$$AUC = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

The logarithmic down trapezoidal method uses logarithmic interpolation between data points to calculate the AUC. For a given time interval (t2 – t1), the AUC can be calculated as follows:

$$AUC = \frac{C_1 - C_2}{ln(C_1) - ln(C_2)}(t_2 - t_1)$$

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AUC [0-72] post dosing will be calculated as the sum of all AUCs from t0 to t72.

AUC [0-72] is calculated using all plasma VEGF-A concentration at planned visits and timepoints. Unscheduled visits will not be used. Time 0 is the Day 1 pre-surgery. Then values at 3, 6, 24, 34, 48 and 72 hours are used in the calculation. The Time used in the above formula is not the scheduled hours but the real time of sample collection as reported in the CRF.

Concentration values below the limit of quantification will be considered missing and will not be replaced when calculating AUC [0-72].

7. STATISTICAL METHODS

7.1 General Methodology

Data will be summarized using descriptive statistics, by treatment group and placebo. In addition, demographic and baseline characteristics will be summarized overall.

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

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

For *categorical* variables and unless otherwise specified, the number of subjects with no missing data and 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 *binary* variables the number and percentages of subjects in each of the two categories will be tabulated based on the number of subjects with no missing data.

For *count* variables descriptive statistics will be similar to the continuous variables.

For continuous variables these summaries will be provided for the observed values and the absolute changes from baseline.

For log-normal variables these summaries will be provided for the observed values, the changes from baseline and the ratio from endpoint to 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. The on-treatment value can be either the value

at a certain time point, or the minimum/maximum value which has been observed during a study period.

Data will be analysed using the following statistical models where appropriate:

Mixed Model Repeated Measures (MMRM)

Fixed factors of the model will be:

- treatment,
- visit,
- treatment*visit interaction.

The covariate (considered also as fixed) will be:

- baseline value.

Visit within patient will be considered as repeated measurements. Baseline covariate will be also log-transformed in case of log-normal variable.

The model will use the Spatial Power Covariance Structures SP (POW) structure for unequally spaced data variance-covariance matrix as default. Unless otherwise specified, scheduled day will be used as visit factor. In case of convergence issues the Compound Symmetry (CS) structure will be used; if the model still not converging, the ANCOVA model below will be used instead. The overall p-value for the treatment-by-visit interaction will not be displayed.

ANCOVA

Fixed factors of the model will be:

- treatment,

The covariate (considered also as fixed) will be:

- baseline value.

Baseline covariate will be also log-transformed in case of log-normal variable.

The reportable results for both the models, MMRM and ANCOVA, for *normal* variables will be:

- Descriptive statistics (n, mean, SD, min and max) of the change calculated as [Visit value - Baseline value] for each group;
- The least square means (LSmeans) and standard errors (SE) for each group;

- The difference between active groups and placebo (LSmeans) together with the SE and confidence Interval (CI) of the difference;
- P-value.

The reportable results for both the models, MMRM and ANCOVA, for *log-normal* variables will be:

- Descriptive statistics (n, GeoMean, GeoCV, min and max) of the Ratio from endpoint to baseline calculated as the exponent of the logarithmical transformation of the Visit value minus the logarithmical transformation of the Baseline value for each group;
- Back transformed LSmeans (which correspond to the ratio between visit and baseline) for each group;
- The ratio between active groups and placebo together with CI of the ratio;
- P-value.

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

For both models, pairwise comparisons (between each active group and placebo) will be assessed in the same model. Two sided 95% CIs will be presented, and p-values will be unadjusted.

If the model does not converge the convergence issue will be detailed in the table.

SAS® Version 9.4 or higher will be used.

7.2 Adjustments for Covariates

When applicable for the analyses of exploratory variables, the baseline value will be used as a covariate.

7.3 Handling of Dropouts or Missing Data

If a patient withdraws prematurely (before Visit 7) from the study, they will be replaced to achieve 7 evaluable subjects in each treatment group.

Unless otherwise stated, missing data will not be replaced.

Partial missing dates will be imputed for AE start date, AE become serious date and AE / Concomitant medication (CM) stop date. No other imputations will be performed. Imputation rules are described below:

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Imputation of Adverse Event Start Date / AE become serious date:

Missing AE start dates (where in eCRF UN, UNK and 0000 indicate unknown or missing Day, 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 01-MMM-YYYY. 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 01-JAN-YYYY 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 start date is after a complete AE end date (or date of death), the imputed start date will be the same as the complete AE end date (or date of death).

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

Imputation of Adverse Event / Concomitant Medication Stop Date:

- 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 31-DEC-YYYY.

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. If the AE/CM is ongoing, the stop date will remain missing. Except for the above and unless otherwise specified, missing data will not be imputed.

7.4 Interim Analyses and Data Monitoring

There will be no interim analysis.

After each sentinel cohort a review of the blinded clinical data and AE and SAE data available after the 1-month follow-up visit (Visit 5) from the current cohort and the available

data from previous cohorts, will be done. Two safety reviews will be performed in parallel as detailed below.

The SRB will be comprised of the following mandatory (voting) members:

- AstraZeneca (Study) Physician;
- AstraZeneca Patient Safety Physician;
- National coordinating investigator;
- Principal Investigator(s) (PIs) from the site(s) that had subjects included in the cohort being evaluated.

Additional experts may participate as non-voting members. The SRB will give recommendation on continuing, temporarily pause (for further evaluation of data), escalating and/or stopping dosing.

Safety Review Committee

As a parallel process, a study independent unblinded SRC consisting of a combination of internal AZ expertise and external experts will review the same set of data and in addition have access to randomisation list. The SRC decide on continuing, temporarily pause (for further evaluation of data), escalating and/or stopping dosing. The composition of the committee will be such that the external experts will be in majority during the vote.

As a parallel process, a study independent unblinded SRC consisting of internal AZ expertise will be consulted regarding safety findings and give input and recommendations to the SRB.

The details of the safety reviews will be provided in separate charters.

The safety outputs required for the SRC will be authored by the Covance programming team. To maintain the blind, the programs will be developed using the available data with a dummy random scheme. The SRC will receive the patient randomisation information from Parexel (AZRand) and there is no requirement for involving Covance Biometrics unblinded team.

Data Monitoring Group

In addition to the existing blinded and unblinded safety review after each sentinel cohort, the unblinded DMG will perform data review on emerging safety and clinical data. This DMG will consist of internal AstraZeneca employees independent of the study team. Internal clinical project and business decision separate from the study will be considered for the clinical development program.

The deliveries would consist of the same data as required for safety review and additionally the following categories:

- 15O PET and CT angiogram;

- Echocardiography and Stress Echocardiography (optional LAD CFVR)

7.5 Multi-centre Studies and Pooling of Centres

This is a multi-center study conducted at up to 4 sites, initially in 1 country but with the possibility to expand to further countries if needed. Twenty-four (24) subjects scheduled for elective bypass surgery will be randomised to ensure at least 21 evaluable subjects. Accounting for replacement subjects it is estimated that up to approximately 33 subjects may be randomised.

Given the low number of sites and countries involved in the study randomisation was not stratified by site or country. In addition, the analysis will be primarily descriptive in nature and data from all sites and countries will be pooled throughout. Country and treatment-by-country interaction will not be included in any model, nor site or treatment-by-site interaction.

7.6 Multiple Comparisons/Multiplicity

Not applicable to this study.

7.7 Examination of Subgroups

None for this study.

8. STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The following summaries will be provided:

- The total number of enrolled subjects (signed the informed consent) and the number of subjects who were not randomised (date of randomisation is totally missing) will be provided overall. The number and percentage of randomised subjects will be provided by treatment group and overall.
- The number and percentage of treated subjects (Safety Analysis Set) will be summarized by treatment group and overall for all randomised subjects.
- The number and percentage who did not receive the treatment will be summarized by treatment group and overall for all randomised subjects.
- The number and percentage of treated subjects (Safety Analysis Set) who completed the treatment and those who discontinued treatment prematurely, and the reasons for treatment discontinuation will be provided by treatment group and overall for the randomised subjects.
- The number and percentage of treated subjects (Safety Analysis Set) who completed the study and those who discontinued from the study, and the reasons for study discontinuation will also be provided by treatment group and overall for the randomised subjects.

Primary Reason for ending treatment prematurely are:

- "Adverse event";
- "Subject decision";
- "Severe non-compliance to protocol";
- "Other".

Primary Reason for ending study prematurely are:

- "Death";
- "Withdrawal by subject";
- "Other";
- "Due to COVID-19 pandemic".

Additionally, the number of subjects included in the Safety Analysis Set (see Section 8.3), and the number of subjects excluded from the Safety Analysis Set will be reported together with the number of subjects included in the Exploratory Analysis Set (see Section 8.3), number of subjects excluded from the Exploratory Analysis Set with a break down by reason for exclusion will be provided by treatment group and overall.

A listing of all subjects who discontinued the study after enrolment will be provided using all enrolled subjects.

Subjects excluded from safety analysis set will be also listed for All randomised subjects.

Subjects excluded from exploratory analysis set will be also listed for All randomised subjects.

A listing of randomisation codes for each patient as well as the treatment group they were randomised to will be provided for all randomised subjects. In addition, various batches of IP will be provided for all randomised subjects.

8.2 Protocol Deviations

Important protocol deviations (IPDs) will be summarized and listed for all randomised subjects.

The number and percentage of subjects with at least one IPD category as well as the number and percentage of subjects meeting each IPD category (including COVID-19 pandemic sub selection) will be provided by treatment group and in total.

Subjects meeting an IPD category more than once will be counted once for the corresponding IPD category. Any patient who have more than one IPD category will be

counted once in the overall summary. A listing of IPD categories and sub-categories will be provided.

The list of IPDs is provided in the Non-compliance Handling Plan (NHP) Version 4.0 dated 18 September 2020 or higher.

8.3 Analysis Populations

There will be 4 analysis populations defined for the study analyses.

8.3.1 All Enrolled Subjects

All enrolled subjects will include those who have signed the informed consent form (consent signed date not totally missing).

8.3.2 All Randomised Subjects

All randomised subjects will include those who were randomised (randomised date not totally missing). All randomised patients will be used according to the treatment which the patients were randomised.

8.3.3 Safety Analysis Set

The Safety Analysis Set will include all subjects who were randomised and received at least one injection of IP (date of the treatment started is not totally missing). Subjects will be analysed according to the treatment which they actually received.

8.3.4 Exploratory Analysis Set

The exploratory analysis set will consist of all randomised subjects who received at least one injection of IP and for whom at least one of the exploratory assessments is available for pre-dose and at least one post-dose measurement. Subjects will be analysed according to the treatment to which they were randomised.

8.3.5 Intent-to-Treat (ITT) Population

Not Applicable.

8.3.6 Per Protocol (PP) Population

Not Applicable.

8.3.7 Pharmacokinetics (PK) population

Not Applicable.

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8.4 Demographic and Other Baseline Characteristics

All demographics baseline summaries will be presented by treatment group and overall and will be based on the Safety Analysis Set unless otherwise stated. Age, weight (kg), height (cm) and BMI (kg/m2) will be summarized with descriptive statistics for continuous variables. Age group (<50; >=50 -<65; >=65 years), sex, BMI group (Normal <25; Overweight >=25-<=30; Obese >30 kg/m2), race and ethnic group will be summarized as categorical variables.

Demographic and other baseline characteristics will be presented in listings for all randomised patients.

Patient recruitment by country and center will be summarized by treatment and overall for All randomised subjects. Patient recruitment will be listed for all randomised subjects.

Relevant medical and surgical history will be coded in MedDRA version 20.0 or higher and will be summarized by System Organ Class (SOC) and Preferred Term (PT) for all randomised subjects. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Relevant medical and surgical history will be sorted alphabetically by SOC and PT.

8.5 Prior and Concomitant Therapy

The World Health Organization Enhanced + Herbal Dictionary (WHO-DDE + HD) Drug Dictionary version 2017Jun B3 or higher will be used to classify medications by PT and 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 stop date on or after the first dose of study drug, or any medication taken prior to study drug and that is ongoing.

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

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

Frequency counts and percentages will be provided to summaries the use of allowed and prohibited concomitant medications on all randomised subjects. The number and percentage of subjects within ATC level 4 (chemical subgroup) and product name will be presented by

treatment group and overall. Subjects will only be counted once per ATC level 4 and product name. Allowed concomitant medications will be sorted by decreasing incidence overall, by ATC level 4 and within that by product name.

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

A listing of previous and concomitant medications with ATC codes by WHO-DDE + HD preferred name, route of administration, frequency and dose, start date, duration and reason will be provided for all randomised subjects.

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

8.6 Analysis of Efficacy Parameters

Not Applicable.

8.7 Analysis of Safety

8.7.1 Extent of Exposure and Compliance to Study Treatment

Extent of Exposure

A listing of administration of investigational product will be provided for safety analysis set.

Measurements of Treatment Compliance

Not applicable.

8.7.2 Adverse Events

Unless specified otherwise, AEs will be summarized using the Safety Analysis Set by treatment group and treatment phase as defined in Section 6.2.3 for the on-treatment and follow-up phases. Where number and percentage of subjects are displayed for each System Organ Class (SOC) and within each SOC by Preferred Term (PT), subjects with multiple events in the same PT are counted only once in that PT. Subjects with events in more than 1 PT are counted once in each of those PTs.

AE will be summarized as described below.

An overview table for the following AEs will be produced.

- Number and percentage of subjects with AEs,
- Number and percentage of subjects with AEs leading to death,

- Number and percentage of subjects with SAEs,
- Number and percentage of subjects with AEs leading to study drug withdrawal – for the on-treatment phase only,
- Number and percentage of subjects with AEs leading to study withdrawal.

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

The number and percentage of subjects with any AEs will be displayed by PT and maximum reported intensity. If a subject has multiple events occurring in same PT within a treatment phase, then the event with the highest intensity will be counted.

The number and percentage of subjects with any AEs will be displayed by PT and investigator's causality assessment. If a subject has multiple events occurring in same PT, then the event with the maximum reported causality will be counted.

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

The number and percentage of subjects with AEs with outcome of death and SAEs will be also displayed by SOC and PT.

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

In addition, a list of key subject information for subjects with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP will be provided, including age, sex, event term as reported by the investigator and PT and data related to the event. Time from first dose to AE (in days) will be calculated as the AE start date minus date of dose +1. Time from first dose to death (in days) will be calculated as the date of death minus date of dose +1. The same approach will be used for deriving time from start of treatment to AE becoming serious. Durations will be calculated only for fully completed dates.

The number and percentage of subjects with non-serious AEs in any treatment group will be displayed for each SOC and 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 be presented by patient for all AEs using the Safety Analysis Set.

8.7.3 Clinical Laboratory Evaluations

Laboratory test results for hematology, coagulation and clinical chemistry will be summarized in SI units with n, mean, median, SD, minimum, and maximum for each

treatment group, at each visit and for change from Baseline to each visit by treatment group using the Safety Analysis Set.

For hematology, coagulation and clinical chemistry laboratory parameters, shifts from baseline to minimum/maximum value during treatment using normal reference ranges categories (low, normal and high) will be provided.

In addition, hematology, coagulation and clinical chemistry laboratory variables treatment-emergent changes will be summarized by treatment group using the Safety Analysis Set including the number and percentage of subjects for the categories of increase, decrease, and increase and/or decrease.

Subjects with potential Hy's Law selected as described in section 6.7.3 will be provided in listing format for the Safety Analysis Set.

The number and percentages of maximum ALT and AST by maximum total bilirubin will be also provided by treatment group for the Safety Analysis Set for on-treatment phase and follow-up phase, using the following categories:

Bilirubin
< 2xUpper limit of normal (ULN)
≥ 2xULN
ALT
< 3xULN
≥ 3 - < 5xULN
≥5 - < 10xULN
≥10xULN
AST
< 3xULN
≥ 3 - < 5xULN
≥5 - < 10xULN
≥10xULN

All clinical laboratory data will be presented in listings for the Safety Analysis Set and within each listing, quantitative laboratory values outside the normal ranges will be flagged.

8.7.4 Other Observations Related to Safety

Vital Signs

Vital signs [pulse (bpm), pulse oximetry (%), and systolic and diastolic blood pressure (mmHg)] will be summarized descriptively as continuous variables with n, mean, median,

SD, minimum, and maximum, at each visit and for change from Baseline to each visit by treatment group using the Safety Analysis Set. This will not be performed for pre and post-adenosine vital signs. Vital signs data will be also listed using the Safety Analysis Set.

Electrocardiogram

Shifts from baseline at EoT will be analysed using the Safety Analysis Set and by treatment group, as no change from baseline (including normal to normal, abnormal clinically significant (ACS) to ACS and abnormal not clinically significant (ANCS) to ANCS), ACS to ANCS, ACS to normal, ANCS to normal, normal to ANCS, normal to ACS, and ANCS to ACS. ECG data will be listed using the Safety Analysis Set.

Physical Findings

PE will be presented in listing format for the Safety Analysis Set.

Hemopericardium and/or tamponade assessment with echocardiography

Hemopericardium and/or tamponade will be provided in listing format using the Safety Analysis Set.

8.8 Pharmacodynamics

As described Section 6.8 except samples taken for analysis of exploratory biomarkers, no other pharmacodynamics samples will be taken. Analyses of exploratory biomarkers are described in Section 8.9.

8.9 Exploratory Analyses

15O PET and CT angiogram

Regional sMBF in the myocardial region that received injections, Global sMBF, Regional MPR in the myocardial region that received injections and Global MPR (mL/g/min) can be considered as Normal distributed. They will be summarized descriptively as continuous variables at each visit including changes from Baseline. Change from baseline is calculated as visit value minus baseline value. Summaries will be presented by treatment group using the Exploratory Analysis Set.

In addition, 15O PET data will be analysed for changes from baseline at visit 6 using the MMRM as reported in Section 7.1 with data from visits 5 and 6. Change from baseline is calculated as visit value minus baseline value. The reportable results will be those for Normal variables described in Section 7.1.

15O PET and CT angiogram data will be presented separately in listing format for all enrolled subjects.

Graphical representations of the absolute values (mean (95%CI)) over time will be provided by treatment group using the Exploratory Analysis Set.

Echocardiography

Echocardiography data are:

- Regional wall motion in the LV segments where IP was received (GLS 1–16),
- cardiac volumes (LVEDV and LVESV),
- LVEF at rest,
- global longitudinal strain at rest.

Stress echocardiography data are:

- CFVR assessments:
  - CFVrest,
  - CFVhy,
  - CFVratio,
- LVEF at stress,
- global longitudinal strain at stress.

All Echocardiography variables will be analysed using the Exploratory Analysis Set.

Except for CFVR assessments, all these variables will be summarized descriptively as continuous variables at each visit including change from Baseline. Change from baseline to each visit will be defined as the visit value minus baseline value.

CFVR assessment variables are log-Normal variables. They will be summarized descriptively by treatment group for all visits for the actual values and for the changes from baseline. The actual values will be summarized as log-normal variables. Change from baseline will be defined as the visit value minus the baseline value and will be summarized using n, mean, standard deviation (SD), median, minimum and maximum.

In addition, echocardiography data will be analysed for changes from baseline at visit 7 using the MMRM reported in Section 7.1 with data from visits 5, 6 and 7.

Echocardiography and stress echocardiography data will be presented in listing format for all enrolled subjects.

d6MTW and MCWS (optional)

No analysis for d6MWT and MCWS is expected as of being optional data and consequently having no data available.

Clinical Outcome Assessments

PRO Questionnaires: KCCQ and SAQ

KCCQ overall summary score and SAQ scores (physical limitation score, angina stability score, angina frequency score, treatment satisfaction score, and quality of life score) are normally distributed and will be summarized descriptively as continuous variables at each visit including changes from Baseline. Change from baseline to each visit will be defined as the visit value minus baseline value.

Summaries will be presented by treatment group using the Exploratory Analysis Set.

In addition, KCCQ overall summary score and SAQ scores will be analysed for changes from baseline at visit 7 using the MMRM as in Section 7.1 with data from visits 5, 6 and 7. Change from baseline to each visit will be defined as the visit value minus baseline value. The reportable results will be those for Normal variables described in Section 7.1.

KCCQ overall summary score and SAQ scores will be presented in listing format for all enrolled subjects.

Graphical representations of the absolute value (mean (95%CI)) over time will be provided by treatment group using the Exploratory Analysis Set.

NYHA Classification

The number and percentage of subjects within each class will be summarized by treatment group at each visit using the Exploratory Analysis Set.

NYHA classification will be presented in listing format for all enrolled subjects.

Exploratory Biomarkers

All exploratory biomarkers analysis will be performed using the Exploratory Analysis Set.

Cardiovascular Biomarkers:

[redacted] are log-Normal distributed variables. [redacted] will be summarized descriptively by treatment group for all visits for the actual values and for the changes from baseline. Change from baseline to each visit will be defined as the visit value minus baseline value.

[redacted] will be also analysed for change from baseline at visit 7 using the MMRM as in Section 7.1 using scheduled hours as visit factor with data from Day 1/3 Hours after first injection, Day 1/6 Hours after first injection, Day 2/24 Hours after first injection, Day 2/34 Hours after first injection, Day 3/48 Hours after first injection, Day 4/72 Hours after first injection, Visits 5, 6 and 7. Change from baseline to each visit will be defined as the logarithmic transformation of the visit value minus the logarithmic transformation of the baseline value.

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The reportable results will be those for log-Normal variables as described in Section 7.1.

[redacted] data will be presented in listing format for all enrolled subjects.

Graphical representations of the absolute values (GeoMean (95%CI)) over time will be provided by treatment group using the Exploratory Analysis Set.

[redacted] concentrations:

VEGF-A protein concentration is a log-Normal distributed variable. It will be summarized descriptively by treatment group for all the nominal visits, for the actual values and changes from baseline. Change from baseline to each visit will be defined as the visit value minus baseline value.

VEGF-A will be also analysed for change from Baseline at Visit 5 using the ANCOVA reported in Section 7.1 with data from visit 5. Change from baseline to each visit will be defined as the logarithmic transformation of the visit value minus the logarithmic transformation of the baseline value. The reportable results will be those for log-Normal variables described in Section 7.1.

VEGF-A protein concentrations data will be presented in listing format for all enrolled subjects.

Graphical representations of the absolute values (GeoMean (95%CI)) in VEGF-A protein concentrations over time will be provided by treatment group using the Exploratory Analysis Set. In addition, graphical representation of individual patient data over time will be provided by treatment group using the Exploratory Analysis Set.

VEGF-A protein, AUC[0-72]

AUC [0-72] will be also summarized by treatment group for the actual values as log-normal variable.

AUC [0-72] will be also analysed using the ANCOVA reported in Section 7.1. AUC [0-72] used for the model will be log-transformed. The baseline used in the model is the value of VEFF-A at t0 (visit 3 day 1 pre-dose). The reportable results will be:

- Descriptive statistics (n, GeoMean, GeoCV, min and max) of the AUC [0-72] for each group;
- Back transformed LSmeans for each group;
- The ratio between active groups and placebo together with CI of the ratio;
- P-value.

8.10 COVID-19 analysis

Additional analyses will be performed to explore the impact of COVID-19 and implemented contingency measures for all randomised subjects. The number and percentage will be provided for the following categories:

- participants discontinued from study or study treatment due to COVID-19
- protocol deviations related to COVID-19.

In addition, the following listings will be provided for:

- participants affected by the COVID-19 related study disruption
- participants with reported issues in the Clinical Trial Management System due to COVID-19 pandemic.

9. Computer Software

All analyses will be performed by Covance using Version 9.4 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

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

10. References

11. Appendices

Appendix 1 Variable definitions

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

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

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

STATISTICAL ANALYSIS PLAN

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Appendix 2 Summary table of statistical models

Parameter	tested visit	Data used	Statistical Model	Test	Alpha level	Normality
Change from baseline in PET measurements						
Regional sMBF in the myocardial region that received injections (tMBFs) (mL/g/min)	6	(B), 5 , 6	MMRM	Two-sided test of difference	0.05	Normal
Global sMBF (gMBFs) (mL/g/min)						
Regional MPR in the myocardial region that received injections (tCFR) (ratio)						
Global MPR (gCFR) (ratio)						
Change from baseline in Echocardiography parameters						
GLS 1 - 16 rest GLS 1 - 16	7	(B), 5 , 6, 7	MMRM	Two-sided test of difference	0.05	Normal
Cardiac volumes rest (LVEDV and LVESV)						
endo GLS rest ENDOG						
LVEF rest LVEF						
Change from baseline in Clinical symptoms.						
KCCQ overall summary score	7	(B), 5 , 6, 7	MMRM	Two-sided test of difference	0.05	Normal
Seattle Angina Questionnaire (Physical limitation score, Angina stability score, Angina frequency score, Treatment satisfaction score, Quality of life score)						
Change from baseline in Exploratory biomarkers						

STATISTICAL ANALYSIS PLAN

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VEGF-A

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AUC 0-72 hours post dosing	AUC 0-72	AUC 0-72	ANCOVA	Two-sided test of difference	0.05	Log-N

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Document Name: d9150c00003-sap-ed3		
Document Title:	Statistical Analysis Plan Edition 3	
Document ID:	Doc ID-004049877	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
12-Oct-2021 13:29 UTC	[redacted]	Author Approval
12-Oct-2021 12:58 UTC	[redacted]	Author Approval

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