Clinical Study Protocol	
Drug Substance	AZD8601
Study Code	D9150C00003
Version	5.0
Date	27 Feb 2020

A randomized, 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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 1.0, 17 Aug 2017
Initial creation
Version 2.0, 26 Feb 2018
"International coordinating investigator" was substituted with "National coordinating investigator" throughout the protocol as for now the study started only in one country. Name of lead investigator was updated accordingly. See Sections Synopsis and 3.11.1.1.
The number of countries was updated to reflect the current situation where the study initially will be conducted in 1 country but with the possibility to expand to further countries if needed. See sections Synopsis and 1.3.1.
Text about digital 6-minute walking test was updated to make the test optional, and to describe an active test instead of only passive and a supervised test being made at the site. Clarification of the variables collected has also been made. See Sections 2.4, 4 (Table 1 and Table 2), 4.1.3 and 5.3.6 and 8.4.2
The text was updated to say that there will be three dose arms: this was a typo in the original protocol since there has always been three arms; low dose AZD8601, High dose AZD8601 and placebo. See Sections Synopsis, 1.3.1 and 1.3.1 (Figure 1).
A correction was made for the allowed time window for Visit 1. The original protocol incorrectly stated that Visit 1 should be done Day ≤ -90. Correctly, it should be done earliest 3 months and latest 15 days before surgery, which means between Day -90 to -15. See Sections 1.4 (Figure 2), 4 (Table 1) and 4.1.2. It was also clarified that visit 3 is Day from -1 to 4 (not only from Day 1) in Section 1.3.1 (Figure 2).
Inclusion criterion 4 was corrected to state: "Indication for elective CABG surgery enrolled at least 15 days before the planned surgery" instead of 2 weeks to be in accordance with time windows given elsewhere in the document. See Section 3.1.
Text was updated to clarify that AstraZeneca Supply chain, but not Call Centre as originally written, will perform the randomization. The process was changed for practical reasons after finalisation of the protocol. See Section 3.5.
A clarification was made: if needed, individual treatment codes for medical emergency unblinding will be available to site Investigators via Contact Call Center, but not physically at the Site. See Section 3.7.

The section about Safety review board was updated to - replace International coordinating investigator with National coordinating investigator - add possibility to involve additional experts as non-voting member - add possibility to temporarily pause dosing for further evaluation of data See Section 3.11.1.1
Table 1 was updated with assessments that have been identified as incorrect or missing in Table compared to text, see Section 4. - Optional AZ activity app: d6MWT, MCWS - Added filming/photo on Visit 3, day 1 (i.e. highlighting already present assessment) - Add X for dECG day -1 - Add X for Concomitant medications and AE on Visit 3, day -1
To make visit planning and conduct more feasible for site and patients the text was updated to allow that Visit 1 and Visit 2 can be done on the same day, except for the PET assessment given that the visit is performed between day -35 to day -15 and the PET assessment is done on day -14 at the latest. See Section 4.1.3 and footnote to Table 1 in Section 4.
[redacted]
[redacted]
Text was updated to specify the process for SAE reporting, if the WBDC system is not available. Not to use telephone, but instead use fax or e-mail. See Section 6.4.
Correction that were identified during development of the Statistical analysis plan has been made in statistics sections, see Synopsis and 8.5.1. A correction was made regarding the definition of an evaluable patient. The original

protocol stated that "An evaluable patient is defined as a patient having completed safety and tolerability assessment at baseline and 1, 3 and 6 months follow up." During development of the Statistical analysis plan the following was considered more appropriate: "An evaluable patient is defined as a patient who has completed the study." See Section 1.3.1. In 8.4.3 the text about VEGF-A protein was corrected in line with other sections to not include visit 6 and 7 assessments.
[redacted]
Minor typographical errors were corrected.
Version 3.0, 8 May 2018
In synopsis the definition of "evaluable patient" was updated to match the change that was made in Section 1.3.1 in version 2.0, as it was missed to change it in synopsis then.
Text was updated to clarify that AstraZeneca Supply chain, but not Call Centre as originally written, will perform the randomization. The process was changed for practical reasons after finalisation of the protocol. See Section 3.5. This was listed as a change already in version 2.0 but it was missed to change the actual text.
Table 1, Section 4 has been modified: - At Visit 3, the pre-surgery timepoint on day 1 for all biomarker samples has been moved to day -1, as it was identified to be unfeasible to take theses samples when the patient was already in the surgery room - At visit 3, a time window of ±1 hour for when the sample can be taken has been added for those samples that have a specified timepoint - Clarification added about BP, pulse and pulse oximetry timing, Visit 3 - Clarification added about dECG timepoints Day 1, Visit 3 - Clarification was added about the telemetry recording at Visit 3 Removed from Table 1 and Table 2 that LAD CFVR is optional to avoid misunderstanding that it may be optional on patient level. In Sections 4.1.2 and 5.3.2.1 it is stated that it should be done if available at the site. Table 2; deleted an empty row with "Hemopericardium and/or tamponade assessment with echocardiography", unnecessary as no assessment is planned in the follow-up period.
Section 5.2.1, Table 3 (Standard Clinical Laboratory Evaluation Panels): clarified for some

assessments if qualitative or quantitative.
In Section 5.2.3 clarification was made concerning use of study specific ECG machines and assessments on Day 1, Visit 3.
Text was updated to specify the process for SAE reporting, if the WBDC system is not available; e-mail address was corrected. See Section 6.4.
Text has been added in 5.3.3 and Appendix F to further describe gyrocardiography in response to request from the Finnish authority Valvira, as it is a new medical device that does not have CE marking yet.
Minor adjustments were done in Section 8 to match Statistical Analysis Plan.
Version 4.0, 22 Jan 2019
In synopsis title has been changed from National Co-ordinating Investigator to International Co-ordinating Investigator, due to study expansion to more countries.
Minor adjustment to text about number of sites and study timelines in Synopsis and 1.4
Adjustment has been done to the allowed time window between Visit 2 and Visit 3 and clarification Reason is that sites can be allowed more flexibility as long as assessments for inclusion are done and pre-operative conference, randomisation procedure, order and delivery of investigational product can be secured before planned surgery date. Text in Section 4 and 4.1.3 has been changed accordingly.
The exploratory gyrocardiography assessment has been removed from the study protocol. The assessment had not yet been implemented. Initially, due to that approval for this unregistered medical device had to be obtained in Finland before implementation. Once approved, it took time before any new patient was enrolled. When new countries are added to the study, it was decided not to include the assessment locally as awaiting approval for unregistered medical device could delay approval of clinical trial application. It was judged that the sample size in Finland only would be too small to evaluate this exploratory assessment and therefore it is excluded completely. Text about gyrocardiography has been removed accordingly in Sections 2.4. 4, 4.1.2, 4.2.1, 4.3.2, 4.3.4, 5.3.3, 8.4.2. Appendix F has been removed completely.
The AstraZeneca activity app for the digital 6-min walk test will not be applicable for the newly added country Germany as it is not feasible to translate the app to German. The app will remain as optional assessment in the other participating countries ([redacted]

[redacted]). This has been clarified in Sections 2.4, 4, 4.1.2 and 5.3.6.
Minor adjustments have been done to the urinalysis assessments. Clinical study site local laboratories are using different methods of urinalysis (quantitative, semi-quantitative, qualitative), making the urine safety evaluation technically complicated. Descriptive statistics might need to be applied to evaluate some of the reported urine laboratory values changes. Therefore, AstraZeneca will provide all study sites with the same type of urine dipstick test kits for assessment of glucose, protein, blood and WBC, to ensure that the urine safety laboratory assessment method within the study is identical across all clinical sites. Creatinine and albumin will still be quantified by the local laboratory. Urine microscopy will no longer be used in the study. As the study is currently expanding to additional countries and sites this is considered to be increasingly important to ensure harmonisation. Sections 4, 5.2.1 and 8.5.1 have been updated accordingly.
Appendix C wording was updated in order to clarify the process of PHL and HL cases reporting in accordance with the FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'.
The CSP has been adjusted to open for the possibility of patients to be enrolled at one site and, if needed, to perform the 15O PET assessment at another, named site. The reason is that suitable patients can be identified at any hospital performing CABG surgery, but few hospitals have the ability to perform the 15O PET. Referring patients for PET would facilitate enrolment. Sections 4.1.3, 4.3.2, 4.3.3 and 5.3.1 have been adjusted accordingly.
In section 5.3.7 text has been adjusted to say that the injection procedure should be either filmed and/or photo taken for documentation purpose. Previous text read like both options was mandatory. Film is optimal but if not possible, photo is enough.
A typo has been corrected in Table 1, Section 4. For blood pressure and pulse oximetry, text erroneously stated that Day 1 four post-surgery assessments done should be done. Corrected to three.
Version 5.0, 27 Feb 2020
The expected study duration has been prolonged to Q1 2022 in the Synopsis section.
Upon submission of this study protocol in Germany, the regulatory authority (Paul Ehrlich Institut) and the local ethics committee requested that the safety review procedure was

updated, so that the unblinded Safety Review Committee included external experts and had decision right about the progress of the study. The process has been adjusted to meet this request. It was also required to add Study specific stopping criteria. In addition, an unblinded Data Monitoring Group (DMG) has been added to enable internal clinical project and business decision separate from the study. Sections 1.3, 1.4, 3.6 and 3.11 have been adjusted accordingly.
To increase operational feasibility for patient and site staff, it has been added that if a patient is referred to another hospital for the 15O PET assessment, CT can also be performed there. Sections 4.1.3, 4.3.2, 4.3.3 and 5.3.1 have been adjusted accordingly.
A cross was missing in Table 1 to indicate that Medical history is to be checked on Visit 3, day -1. This has been adjusted accordingly in Section 4 .
An erroneous sentence has been deleted in Section 7.1. Text previously indicated that each syringe would be labelled with a patient-specific dosing label in local language. Each syringe is not labelled by pharmacy personnel due to a combination of sterility requirement and that syringes are too small to accommodate the labels.

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

CLINICAL STUDY PROTOCOL SYNOPSIS

A randomized, 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

[redacted]

Study site(s) and number of patients planned

The study will be a multi-centre study conducted at [redacted] 4 sites, initially in 1 country but with the possibility to expand to further countries if needed. [redacted]

Study period

Estimated date of first patient enrolled Q4 2017

Estimated date of last patient completed Q1 2022

Phase of development

Phase IIa

Study design

This is a randomized, double-blind, placebo-controlled, sequential design, multicentre study in patients with moderately impaired systolic function undergoing CABG surgery.

Objectives

Primary Objective:	Outcome Measure:
To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery with moderately impaired systolic function.	– Adverse Events/Serious Adverse Events (AEs/SAEs) – Vital signs (blood pressure, pulse) – Electrocardiogram (ECG) – Left Ventricular Ejection Fraction (LVEF) – Physical examination – Laboratory assessments (hematology, clinical chemistry and urinalysis)

Target patient population

Male and female patient scheduled for elective coronary artery by-pass graft (CABG) surgery within the next 3 months, aged 18 years and above, with BMI<35 kg/m^2 who are found eligible for the study after review of the inclusion and exclusion criteria and who have signed Informed Consent Form.

Duration of treatment

At Visit 3 patients will receive either AZD8601 or placebo. AZD8601 will be administered as epicardial injections. [redacted]

Placebo for AZD8601 will be administered in the same manner as AZD8601 and in a volume and injection distance to match AZD8601.

Investigational product, dosage and mode of administration

Investigational product	Dosage form and strength	Manufacturer
AZD8601	AZD8601 solution for injection [redacted]	AstraZeneca
AZD8601	AZD8601 solution for injection [redacted]	AstraZeneca
Placebo	Placebo for AZD8601 solution for injection	AstraZeneca

Statistical methods

Placebo data will be pooled throughout.

Demographic and baseline data will be summarized by treatment and overall.

All statistical analyses and production of tables, figures and listings will be performed using SAS version 9.2 or later.

If not otherwise specified, baseline refers to the last measurement prior to administration of investigational product.

Analysis of the primary variable(s)

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

All safety variables will be summarised by treatment groups and visit using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous data and absolute and relative frequencies for categorical data).

AEs will be summarised by treatment group, treatment related and severity by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT).

Laboratory data for haematology and clinical chemistry will be summarized by treatment group and visit. The number and percentages of patients with haematology and clinical chemistry treatment emergent laboratory changes with respect to normal ranges between baseline and post treatment will be tabulated. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarised by treatment group. Categorical outliers may be presented by numbers but need to be considered in context of inclusion/exclusion criteria. Physical examination and vital signs variables will be summarised by treatment group.

Unless otherwise stated, the following rules will apply to any repeated safety assessments:

- If the repeated measurement of a specific parameter occurs prior to IP administration (Day 1), the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline.

Exploratory analysis

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

All exploratory variables will be summarised by treatment group and visit using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum and geometric mean and geometric SD if applicable for continuous data and absolute and relative frequencies for categorical data). P-values will be unadjusted and tests will be two-sided.

Mean values per treatment will be plotted against visit.

Geometric mean per treatment and individual plasma levels of VEGF-A will be plotted against time after dosing. Calculation of VEGF AUC - Area under the concentration-time curve (µmol*h/L) will be done by linear up/ log down trapezoidal summation.

Change from baseline will be analysed for all exploratory variables with baseline and post-dose measurements. Change from baseline for some exploratory variables will be analysed using Analysis of Covariance, (with treatment as fixed effect, patient as random effect and baseline value as covariates) or a repeated measurements model (with treatment, visit and treatment-by-visit interaction as fixed effects, baseline as covariate and patient as random effect). If an approximation of the variable of interest follows a log-normal distribution rather than a normal distribution, a logarithmic transformation of the variable of interest will be done. All variables that are transformed will be back transformed for reporting.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
15O PET	O-15 Radiowater Positron Emission Tomography
AE	Adverse Event
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
BP	Blood Pressure
CABG	Coronary Artery By-pass Grafting
CAD	Coronary Artery Disease
[redacted]	[redacted]
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
d6MWT	Digital 6-minute Walking Test
DAE	Discontinuation of Investigational Product due to Adverse Event
DGR	Dangerous Goods Regulations
DILI	Drug Induced Liver Injury
DMG	Data Monitoring Group
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
EF	Ejection Fraction
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
hsTNT	High-Sensitivity Troponin T
IATA	International Airline Transportation Association
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
ISRB	Investigational Medicines Safety Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAD	Left Anterior Descending
LCA	Left Coronary Artery
LCX	Left Circumflex
LH	Luteinizing Hormone
LIMS	Laboratory Information Management System
LPLV	Last Patient Last Visit
LV	Left Ventricular
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
MCWS	Maximum Continuously Walked Steps
MedDRA	Medical Dictionary for Regulatory Activities
modRNA	Modified Ribonucleic Acid
MoP	Manual of Procedures

Abbreviation or special term	Explanation
MPR	Myocardial Perfusion Reserve
NA	Not Applicable
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
PD	Pharmacodynamics
PET	Positron Emission Tomography
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PR	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PRO	Patient Reported Outcomes
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RCS	Right Coronary Artery
RR	The time between corresponding points on 2 consecutive R waves on ECG
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQ	Seattle Angina Questionnaire
sMBF	Stress Myocardial Blood Flow
SOC	System Organ Class
SRB	Safety Review Board
SRC	Safety Review Committee
TBL	Total Bilirubin
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

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. In Global Burden of Disease study CAD affected 110 million people globally and resulted in 8.9 million deaths in 2015 making CAD the most common cause of death in a global scale. (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016, GBD 2015 Mortality and Causes of Death Collaborators 2015) 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, (Task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology 2001) with reports suggesting CAD to be the primary cause of heart failure in even close to 70% of cases (Medical Advisory Secretariat 2010). According to recent trends in the United States, in individuals of 40 years and over, half of healthy men and one third of women develop CAD in their life time (Rosamond W et al. 2007). When comparing CAD to heart failure the risk of heart failure is lower but with apparently more detrimental progression of disease - in population of 40 years and over the lifetime risk of developing heart failure is 20% (Djousse L et al. 2009) with approximate survival rate of 50% in 5 years' time after diagnosis (Go AS et al. 2013). 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. (Cohn JN et al 1993, Parameshwar J et al. 1997) 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 (Stirrup J et al. 2017). However, in spite of medical advancements in treatment of especially ischemic heart failure, such as revascularizations (Stirrup J et al. 2017), beta-blockers (Packer M et al. 1996), angiotensin-converting enzyme (ACE) inhibitors,(The CONSENSUS Trial Study Group 1987) angiotensin II inhibitors (Pitt B et al. 1997) and aldosterone receptor blockade, as well as novel devices such as cardiac resynchronization therapy, (Yancy CW et al. 2013), there is a clear unmet medical need in addressing the medical therapies for this patient population.

Through stimulation of angiogenesis, especially arteriogenesis, therapeutic vascular growth is emerging as a concept for management of vascular indications such as coronary ischemia, critical limb ischemia and chronic wounds. 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 (Ferrara N et al. 1991). 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 165 amino acid long primary isoform (VEGF165), 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,

randomized 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 mRNA (modRNA) has been put forward as a non-immunogenic and non-integrating modality for efficient and transient expression of target proteins in mammalian cells. AZD8601 is VEGF-A165 modRNA under development as a novel modality for local production of human VEGF-A protein and is developed for the treatment of ischemic heart disease.

1.2 Rationale for study design, doses and control groups

This study is a randomized, 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 left ventricular ejection fraction (LVEF) going through elective CABG. Prior to CABG, each patient will undergo a O-15 radio-water positron emission tomography (PET)/ Computed Tomography (CT) scan, which generates a combined image of coronary angiogram superimposed on a myocardial perfusion map to locate areas of myocardial ischemia and dysfunction. Whilst ischemic LV systolic dysfunction may be due to myocardial damage, it may also result from the presence of dysfunctional, but viable, myocardium. Such viable tissue, associated with reduced perfusion and diminished contractility at rest that recovers function upon revascularization, has been commonly referred to as hibernating myocardium (Rahimtoola SH 1985, Rahimtoola SH 1989). Revascularization can reach and improve function of hibernating myocardium but most often it may not be able to recover full physiologic functionality. 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 cohort will be explored. For this purpose a PET camera will be utilized to detect changes in myocardial perfusion, and ventricular wall motion (Saraste A et el. 2017) will primarily be assessed by echocardiography.

1.3 Benefit/risk and ethical assessment

This is a first time in patient Phase IIa study aiming to show the safety and tolerability of epicardial injections of AZD8601 in patients with ischemic heart disease undergoing CABG surgery and with moderately impaired systolic function. The study duration with follow-up

until 6 months post CABG surgery is expected to be of sufficient length to permit evaluation of the drug's safety and tolerability profile on top of standard of care in CAD patients to support further clinical development. As explorative objectives, potential effects of VEGF-A [redacted]RNA (AZD8601) on regional and global stress myocardial blood flow (sMBF) and myocardial perfusion reserve (MPR) and cardiac function will be explored.

A prior Phase I study has been conducted investigating AZD8601 induced intradermal VEGF production which suggested a well-tolerated safety profile. There were no apparent clinically relevant trends in blood pressure, heart rate, ECG or laboratory variables, including liver safety parameters. This is in line with prior safety data covering over 10 years' follow-ups in patients with prior treatment with VEGF modalities (Hedman et al. 2009, Muona K et al. 2012, Rosengart TK et al. 2013). The preclinical safety findings are described in detail in the Investigators Brochure. Based on knowledge of the mechanism of action, previous clinical experience and the preclinical safety studies the potential risks will be closely monitored.

No specific harms are anticipated from participating in this trial. Available preclinical and clinical data suggest that the patients may benefit from participation in the study as administration of VEGF-A [redacted]RNA may improve LVEF. In more detail, functional activity of the AZD8601-produced protein was demonstrated as substantial phosphorylation of the VEGF receptor 2 was seen in human umbilical vein endothelial cells exposed to conditioned medium harvested from cells transfected with AZD8601. Furthermore, AZD8601-produced VEGF-A protein was found to induce angiogenesis as evidenced by a trend towards increased total tube area and number of branch points to a similar extent as seen in cells exposed to human recombinant VEGF-A protein. VEGF-A modRNA given as epicardial injection has been shown to improve cardiac function in several animal models of myocardial infarction, ranging from mice (Zangi L et al. 2013), rat and pig. Preclinical toxicological study in pig model of myocardial infarction did not give rise to any safety concerns (see IB). Further, in an ongoing phase I trial where AZD8601 is administered as intradermal injections, AZD8601 was well tolerated without SAEs. In terms of AEs the most common was local transient injection site reaction which is completely reversible (see IB).

Pharmaceutical therapy administered directly in to myocardium can be administered through several different techniques, such as epicardial, endocardial, intracoronary or coronary sinus approaches. For accuracy and reliability the epicardial approach has been considered as method of choice, although its invasive nature and possible induction of arrhythmias balance the scale in comparison to other available administration modalities (Dib N et al. 2011). Due to this essential and invasive nature of epicardial injections in this study placebo vehicles will be injected to differentiate from possible drug delivery-related effects. To be able to evaluate potential beneficial effects of AZD8601 per se, placebo injections are considered to be necessary in the study design (Mathiasen A et al. 2015). The selected placebo controlled design also enables further differentiation with infrequent but possible adverse effects such as pericardial effusion, e.g. for VEGF in individual cases has been associated with pericardial effusions (Karatolios et al. 2012).

Sentinel cohort dosing with evaluation of 1 month safety data by a Safety Review Board (SRB) before proceeding dosing further patients on same dose level, or proceeding to the higher dose level has been included in the design for the safety of the patients. In parallel a study independent unblinded Safety Review Committee (SRC) will perform additional review. 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. The 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 (see 1.3.1 and 3.11.1).

1.3.1 Dosing rationale

There will be three treatment arms. Patients will be randomized 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 randomized to AZD8601 and 4 to placebo. The investigational product will be given as epicardial injections into the accessible ischemic border zone according to a tailor-made individualized injection map (see 4.1.3.1). 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. 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 sufficient to treat the second one as identified by the injection map, the area will be partially treated applying the same injection distance.

The dose will be administered with approximately [redacted] distance with [redacted] epicardial injections per patient, with 200 µL 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. The tailor made individualized injection map will be based on the combined ^{15}O-water ($H_2{}^{15}O$) PET imaging and CT angiogram performed on Visit 2. [redacted]. Thus dose increment per injection site as well as total dose will not exceed [redacted] from the starting dose. Patients receiving placebo will be dosed according to the same rationale but will receive vehicle injections, [redacted].

1.4 Study Design

This is a randomized, double-blind, placebo-controlled, sequential design, multicentre study in patients with moderately impaired systolic function undergoing CABG surgery.

The study will be 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). Further details are given in Section 4.

To achieve 7 evaluable patients in each treatment group (low dose, high dose and placebo), 21 in total – 24 patients will initially be randomized. An evaluable patient is defined as a patient who has completed the study.

The study will include two cohorts of 12 patients each, which will receive either a low or high dose of AZD8601 (see Section 7.2) in a sequential, dose ascending fashion. Within each cohort 8 patients will be randomized to receive AZD8601 and 4 to placebo.

Each cohort will be divided into 3 sentinel dosing cohorts. See Figure 1. The two first will include 2 patients each – 1 patient randomized 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:

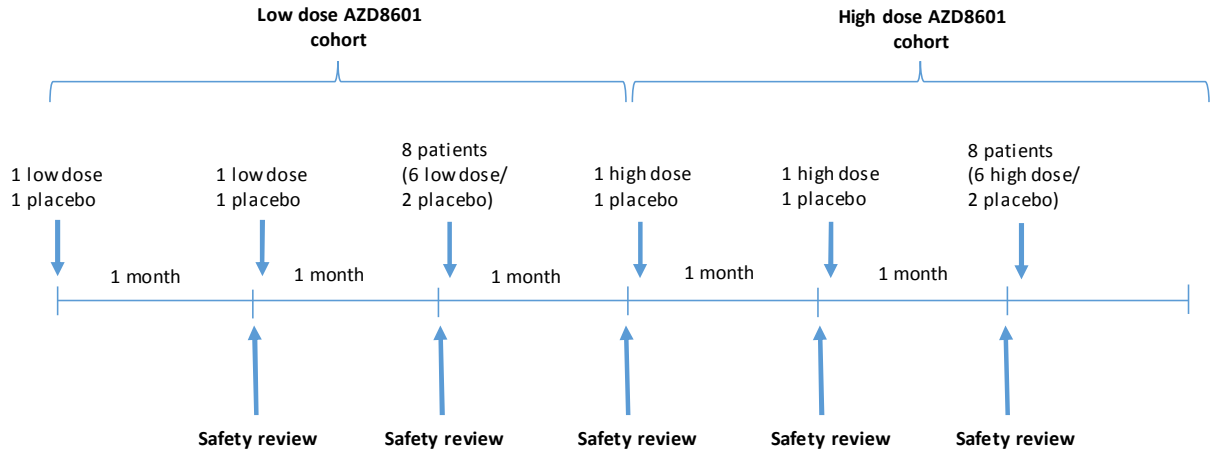
- Blinded safety review board (SRB) consisting of study investigators and AZ personnel
- Study independent unblinded safety review committee (SRC) consisting of a combination of internal AZ expertise and external experts

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. Internal clinical project and business decision separated from the study will be considered for the clinical development program.

This is further described in Section 3.11.1.

For treatment assignment see Section 3.5.

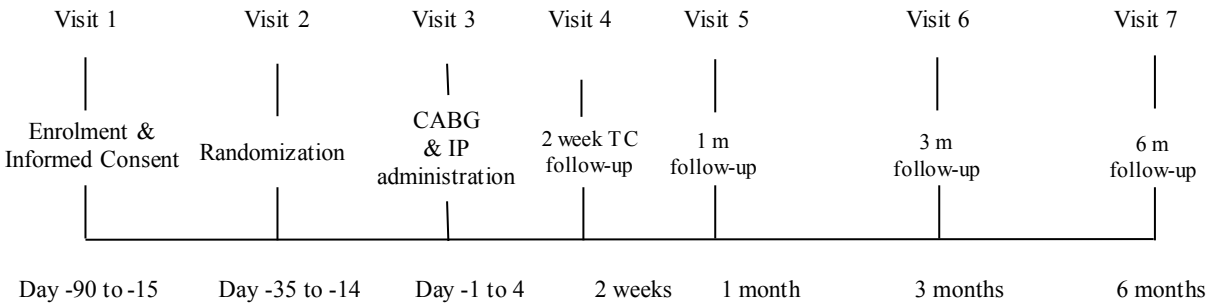
Figure 1 Outline of sentinel dosing cohorts



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 1 and Table 2 in Section 4.

Figure 2 Study flow chart



TC = telephone contact; CABG = coronary artery bypass grafting; IP = investigational product, AZD8601 or placebo; m = month

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery with moderately impaired systolic function.	– Adverse Events/Serious Adverse Events (AEs/SAEs) – Vital signs (blood pressure, pulse) – ECG – LVEF – Physical examination – Laboratory assessments (hematology, clinical chemistry and urinalysis)

2.2 Secondary objectives (NA)

2.3 Safety objectives (NA)

NA due to safety being Primary objective.

2.4 Exploratory objectives

- To assess the effect of AZD8601 in patients undergoing CABG surgery on regional and global sMBF measured with 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 (LVEDV, LVESV) and global 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
- [redacted]
- 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 high-sensitivity Troponin T (hsTnT) and N-terminal pro b-type natriuretic peptide (NT-proBNP) 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 VEGF-A [redacted] RNA (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 digital 6-min walk test (d6MWT) and maximum continuously walked steps (MCWS) parameter and to explore the relationship between these and echocardiographic or other parameters collected here in CAD patients (Not applicable in Germany and any other additional country joining the study)

Note: For details regarding exploratory variables, measurements and analyses refer to Section 5 and subsections, and 8.4.1 to 8.4.3.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

See Section 3.3 for a description of enrolment procedures.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria at Visit 1 and/or 2:

1. Provision of signed and dated informed consent prior to any study specific procedures

2. Males and females:

   a. Males must be surgically sterile or using an acceptable method of contraception (see Section 3.8.5)

   b. Females must be of non-childbearing potential confirmed at screening by fulfilling one of the following criteria a) postmenopausal defined as amenorrhoea

for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels in the postmenopausal range, b) documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

3. Age ≥18 years

4. Indication for elective CABG surgery enrolled at least 15 days before the planned surgery

5. Moderately reduced global LVEF at rest (30% ≤ LVEF ≤ 50%) from medical records

6. If patient is on statin, ACE inhibitor/ARB, and/or beta-blocker, the dose should be stable at least 2 weeks prior to Visit 1

7. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of AZD8601.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Previous randomisation in the present study

3. Participation in another clinical study with an investigational product during the last 3 months

4. BMI > 35 kg/m^2 OR poor image window for echocardiography

5. Need for CABG emergency operation. (Emergency operation is defined as significant symptom status worsening in CAD, such as crescendo angina, unstable angina or ACS requiring rescheduling the revascularization. CAD should be stable at least 3 months prior to Visit 3.)

6. History of ventricular arrhythmia (≥ Lown III) without Implantable Cardiac Defibrillator (ICD)

7. History of any clinically significant disease or disorder which, in the opinion of the PI, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study

8. Severe co-morbidities that can interfere with the execution of the study, interpretation of study results or affect the safety of the patient, in judgement of the investigator

9. eGFR ≤ 30 mL/min (derived from creatinine clearance, calculated by local lab)

10. For CFVR (Visit 1) and sMBF (Visit 2) measurement:

    - Known severe adverse reactions to adenosine
    - Known elevated intracranial pressure
    - AV block ≥ second degree and/or sick sinus syndrome in patient without pacemaker
    - Heart rate < 40 bpm (ECG verified)
    - Systolic blood pressure < 90 mmHg
    - Asthma or COPD with strong reactive component in judgement of investigator
    - Treatment with dipyridamole (e.g. Persantin or Asasantin), theophyllamine or fluvoxamine that cannot be paused

11. Inability to comply with the protocol

12. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity to drugs with a similar chemical structure or class as study drugs

13. Patients unable to give their consent or communicate reliably with the investigator or vulnerable patients e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order

14. Positive hepatitis C antibody hepatitis B virus surface antigen or hepatitis B virus core antibody or human immunodeficiency virus, at Visit 1

15. Known history of drug or alcohol abuse

16. Any concomitant medications that are known to be associated with Torsades de Pointes

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

18. Congenital long QT syndrome

19. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3).

20. Current atrial fibrillation as well as paroxysmal atrial fibrillation.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. In this study, this will include all patients at the clinic scheduled for elective CABG surgery and for whom the medical records were screened to check if they might be eligible for the study.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign potential patient a unique enrolment number, beginning with 'E#'.

3. Determine patient eligibility. See Section 3.1 and 3.2.

4. Assign eligible patient unique randomisation code as obtained from call centre (see Section 3.5)

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

It is estimated that 24 patients need to be randomized and receive treatment in order to achieve 21 evaluable patients who complete safety and tolerability assessments, including echocardiography, at baseline and 1, 3 and 6 months follow up. If a patient withdraws prematurely (before Visit 7) from the study they will be replaced to achieve 7 evaluable patients in each treatment group. Accounting for replacement patients it is estimated that up to approximately 33 patients may be randomized.

If a patient is replaced, then a new enrolment code and randomization code will be assigned. The replacement patient will be assigned to the same treatment as the discontinued patient using the next available randomization code that corresponds to the specific treatment.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study. If a patient is withdrawn prior to dosing, he/she will be replaced.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding the appropriate follow-up of the patient (discontinuation of IP is not an option after Visit 3). The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Upon completion of the randomization requirements specification, the randomization will be produced by Parexel using the AstraZeneca randomization solution (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 cohort 2 patients will be randomized to placebo or AZD8601 at a ratio of 1:1. In the third sentinel cohort 8 patients will be randomized to placebo or AZD8601 at a ratio of 1:3.

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 randomization code having the same treatment allocation.

AstraZeneca Supply Chain will assign randomisation codes.

3.6 Methods for ensuring 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 randomization scheme during the conduct of the study, with the following exceptions:

- AZRand generating the randomization 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 (see 3.11.1.2)
- 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 (see 3.11.1.3)

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

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized 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 randomization. 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 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.

3.8 Restrictions

Restrictions for the study are listed in sections below.

AstraZeneca should be contacted if the investigator is informed of any restriction violations. AstraZeneca will decide whether a patient with restriction violation will be allowed to continue study participation.

Any restriction mentioned below before Visit 1 and signed ICF are up to the patient upon information given per telephone.

3.8.1 Medications restrictions

Abstain from taking any medications contraindicated in the study protocol. For the list of medications prohibited during the study refer to Section 7.7.

3.8.2 Dietary restrictions

Patients should fast overnight from 22:00 hours the evening before Visit 1, 2, 5, 6 and 7. Before Visit 1 and signed ICF, fasting is up to the patient upon information given per telephone.

3.8.3 Alcohol, Drugs of abuse, Tobacco and Caffeine Restrictions

Patients should:

- abstain from caffeine containing drinks for 24 hours preceding the visits when adenosine infusion is given (Visits 1, 2, 5, 6 and 7)
- abstain from smoking for at least 1 hour prior to sMBF measurements, or whenever study procedures demand it. No nicotine substitutes will be offered.
- abstain from drugs of abuse during the entire study.
- abstain from alcohol 72 hours before clinical visits

3.8.4 Exercise restrictions

Patients should avoid intensive endurance training (e.g. running) 48 hours before Visits 2, 5, 6 and 7.

3.8.5 Restrictions for male patients

Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier methods [condom or occlusive cap] in conjunction with spermicides) for the duration of the study (from the time they sign ICF) and for 3 months after administration of IP (AZD8601/matching placebo) to prevent pregnancy in partners.

Sperm Donation: Male patients should not donate sperm for the duration of the study and for at least 3 months after IP administration.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment. However, as the study is designed so that the patient is administered IP on one occasion during CABG (Visit 3), it is only possible for the patient to decide to discontinue IP before any IP is given.
- An adverse event that, in the opinion of the Investigator or AstraZeneca, warrants discontinuation from further dosing
- Patient noncompliance that, in opinion of the Investigator or sponsor, warrants withdrawal (e.g. refusal to adhere to scheduled visits)
- Risk to the patient as judged by the Investigator and/or AstraZeneca.

If the patient is discontinued from IP (i.e. injections stopped during CABG), the scheduled study visits, data collection and procedures should continue according to the Clinical Study Protocol (CSP) until study closure (i.e. Visit 7). Alternatively, if the patient does not agree to

this option, a modified follow up through e.g., regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. The approach taken should be registered in the CRF.

If patient is required to discontinue the IP, every reasonable effort should be made for the patient to remain in the study for appropriate follow-up.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. However, as the study is designed so that the patient is administered IP on one occasion during CABG (Visit 3), it is only possible for the patient to decide not to receive IP before any IP is given.

After IP has been given, the patient is still free to withdraw from the study (i.e. further assessments) although the intention is to keep the patient in the study for follow-up until Visit 7 has been completed. If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are enrolled patients (i.e. signed ICF) who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Screen failure'(the potential patient who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomized patients). 'Failure to meet randomization criteria' should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomized group (it is only applicable for randomized studies and should be used for patient withdrawal post-screening).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. Any mobile phone that has been provided to the patient for d6MWT and MCWS will be returned.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will be replaced to achieve 7 evaluable patients in each treatment group (low dose, high dose and placebo), 21 in total.

3.10.3 Specific withdrawal criteria between visit 2 and 3

Between Visit 2 assessments at site and IP administration at visit 3, a pre-operative cardio-thoracic surgery conference to decide dosing regimen will take place (see Section 4.1.3.1). 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 randomized or receive IP.

If substantial changes of patient status are identified between visit 2 and 3, that are not considered to be consistent with continuation of the study, as judged by the investigator, the patient may also be withdrawn before any IP is administered.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

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

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

The Sponsor reserves the right to terminate the study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Inability to enroll sufficient patients into the study
- Good Clinical Practice (GCP) compliance issues that compromise the validity of the study
- Determination by the SRB or/and SRC (see Section 3.11.1) that the safety of the patient is at risk

The safety and tolerability stopping criteria take into account that each dosing group will have 8 patients on IP and 4 patients on placebo (i.e., 2:1 ratio).

Study stopping criteria

The study can be stopped if 4 or more patients on IP than on placebo, per dose cohort have

- intolerable AEs (death or other unexpected SAEs)

and/or

- clinically significant CABG linked AEs causally related to IP
  - Re-operation (due to pericardial effusion, bleeding, other reasons)
  - Severe arrhythmias (requiring advanced cardioversion)
  - Cardiogenic shock
- Postoperative Ventilation ≥ 48 hours

3.11.1 Safety Review

After each sentinel cohort a review of the blinded and unblinded 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 done in parallel as detailed below.

For criteria for discontinuing IP and withdrawing patients from study on individual level, see Section 3.9.

[redacted]

4. STUDY PLAN AND TIMING OF PROCEDURES

The schedule of assessments for the study is given in Table 1 and Table 2.

Table 1 Schedule of Assessments: Enrolment and treatment periods

	Screening/ Enrolment	**Randomization**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**[1]	**Visit 2**[1]	**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							See Table 4, 5.2.1
Nicotine use	x							Previous and current
Height	x							
Weight and BMI	x							
FSH and LH sampling	x							Females only, see Table 3, 5.2.1
Randomization		x						After the pre-operative cardio-thoracic surgery conference, see 4.1.3.1
IP administration				x				
Safety and tolerability:								

	Screening/ Enrolment	**Randomization**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**[1]	**Visit 2**[1]	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
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 Days 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 Day 1-4 Day 1, one assessment done pre-surgery and three post-surgery. See 5.2.4.1
dECG with digital source file	x	x	x	x	x	x	x	V3: Once Day -1 as baseline, 2 times/day Day 1-4. Day 1 both timepoints will be post-surgery. See 5.2.3
Telemetry			x	→				Start on Day -1, pause during CABG, re-start post-surgery and continue until discharge. See 5.2.3
Physical examination	x (brief)	x		x				See 5.2.2

	Screening/ Enrolment	Randomization	CABG surgery & IP administration					Notes
Visit	**Visit 1[1]**	**Visit 2[1]**	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Blood and urine samples for safety laboratory evaluations	x		x				x (at discharge)	See Table 3, 5.2.1
Hemopericardium and/or tamponade assessment with echocardiography							x	See 5.2.5.1
Exploratory Assessments								
[redacted]				x				[redacted]
15O PET (sMBF)		x						See 5.3.1 At visit 2, PET can be done on a separate day if more feasible
CT angiography		x						See 5.3.1
Echocardiography	x							See 5.3.2
[redacted]	x							[redacted]

	Screening/ Enrolment	Randomization	CABG surgery & IP administration					Notes
Visit	**Visit 1**[1]	**Visit 2**[1]	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
Optional. AZ activity app: d6MWT, MCWS (N/A in Germany and any other additional country joining the study)		x						See 5.3.6 Timepoint of supervised d6MWT to be noted in eCRF.
KCCQ	x							See 5.3.4.1
Seattle Angina Questionnaire	x							See 5.3.4.2
NYHA classification	x							See 5.3.5
Exploratory Biomarkers								
Blood sampling for [redacted]	x	x	x	x	x	x	x	At V2: Only collected if time between V1 and V2 is >2w. At V3: Pre-surgery Day -1. Post-surgery 3, 6, 24, 34, 48 and 72 h after first epicardial injection.[2] See 5.7

	Screening/ Enrolment	**Randomization**	**CABG surgery & IP administration**					**Notes**
Visit	**Visit 1**[1]	**Visit 2**[1]	**Visit 3**					
Day	**-90 to -15**	**-35 to -14**	**-1**	**1**	**2**	**3**	**4**	
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] See 5.7
Plasma samples for future exploratory analysis of AZD8601 (VEGF modRNA) to be stored in biobank			x	x		x		Pre-surgery Day -1. Post-surgery 1, 3 and 48 h after first epicardial injection. [2]
Plasma samples to be stored in biobank for potential exploration of anti-drug immunogenicity		x						See 5.7
Plasma samples to be stored in biobank for potential exploratory analyses	x			x		x	x	See 5.7 V3: 6, 48 and 72 hours after first epicardial injection. [2]

[1] Visit 1 and Visit 2 can be combined, however PET and CFVR (if applicable) assessments should be done on separate days see 4.1.3

[2] Post- surgery samples should be taken as close to the specified timepoint as possible, but a time window of ± 1 hour is allowed.

Table 2 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	Incl herbal/ nutritional supplements
Safety and tolerability:					
Adverse event review	x	x	x	x	
Blood pressure and pulse		x	x	x	Supine. See 5.2.4.1
dECG with digital source file		x	x	x	See 5.2.3
Physical examination		x	x (brief)	x (brief)	See 5.2.2
Blood and urine samples for safety laboratory evaluations		x	x	x	See 5.2.1
Exploratory Assessments					

	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)**	
15O PET (sMBF)		x	x		See 5.3.1
CT angiography			x		See 5.3.1
Echocardiography		x	x	x	See 5.3.2
[redacted]				x	See 5.3.2.1
Optional. AZ activity app: d6MWT, MCWS (N/A in Germany and any other additional country joining the study)		x	x	x	See 5.3.6 Timepoint of supervised d6MWT to be noted in eCRF.
KCCQ		x	x	x	See 5.3.4.1
Seattle Angina Questionnaire		x	x	x	See 5.3.4.2
NYHA classification		x	x	x	See 5.3.5
Exploratory Biomarkers					
Blood sampling for hsTnT and NT-proBNP		x	x	x	See 5.7

	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)**	
Plasma samples for VEGF-A protein analysis		x			See 5.7
Plasma samples to be stored in biobank for potential exploration of anti-drug immunogenicity		x	x	x	See 5.7
Plasma samples to be stored in biobank for potential exploratory analyses		x	x	x	See 5.7

Order of assessments:

NB: 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 (BP, 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, [redacted]
6. 15O PET/CT angiogram
7. Post-surgery blood samples

4.1 Screening/Enrolment period

4.1.1 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 to Visit 1 but before signing of ICF this is up to the patient.

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

If a patient is found potentially suitable, he/she will be asked about participation in this study. Before any study related procedures are conducted, the patient will receive information about the study and will be asked to sign ICF.

Patients will undergo baseline assessments of echocardiography parameters including stress cardiac function measurement. Only patients with acceptable adenosine tolerance, defined as stable hemodynamically and able to tolerate adenosine-related symptoms during adenosine infusion, will be included. [redacted]

Kansas City Cardiomyopathy Questionnaire (KCCQ), Seattle Angina Questionnaire and NYHA class will be used for assessment of clinical symptoms (see Sections 5.3.4.1, 5.3.4.2, 5.3.5)

For other assessments that will be performed at Visit 1, see the schedule of assessment, Table 1, Section 4.

4.1.3 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. If the 15O PET is not available at the hospital where the patient is enrolled, the patient will be referred to another hospital for this assessment only; however, the CT scan may also be performed at the site of the 15O PET scan if required.

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, [redacted]

Please note: the timeframe between PET assessment and the date of planned CABG optimally 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 of the inclusion criteria and none of the exclusion criteria will be randomized at this visit.

The patient will be fasting on arrival to the clinic.

Baseline assessments of rest and stress MBF by 15O PET will be done. Patients will undergo a 15O PET and contrast-enhanced 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. During this visit patients will be provided with a mobile phone (unless they have a suitable iPhone already) and given access to a mobile software application (app) that will be used to conduct the d6MWT and MCWS. The app will be activated on-site at visit 2 and a supervised d6MWT will take place. For further information see Section 5.3.6. (N/A in Germany and any other additional country joining the study.)

Randomization will take place after the outcome of the pre-operative cardio-thoracic surgery conference is available, as described in 4.1.3.1. 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 1.

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

Based on quantitative coronary angiogram and PET/CT perfusion map available from Visit 2, consensus will be reached regarding surgical procedure individualized for each patient. Based on the ischemic area (regions with sMBF < 2.3±0.3 mL/g/min or < 80±10% of the segment with highest sMBF) identified on PET scan and coronary artery morphology by CT-angiogram, 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 LCA territory, starting with the largest ischemic area, i.e. either left anterior descending LAD or LCX supply territory. If the number of injections remaining after complete treatment of the first largest ischemic area is not sufficient 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, where the following are mandatory:

- Responsible thoracic surgeon, PET physician and cardiologist at the local site

- PET core lab responsible and at least one more thoracic surgeon from another hospital

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 randomized or receive IP.

4.2 Treatment period

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

At Visit 3, the patient will come to the clinic and undergo assessments as outlined in Table 1.

During the operation, following by-pass grafting immediately before reperfusion, patients will receive 30 epicardial injections of the treatment they have been randomized to: placebo or any of two different doses of AZD8601 (see Section 7.2). The injections will be given under cardioplegia into all accessible ischemic border zones according to the individualized injection map agreed beforehand (see 4.1.3.1). The actual injection procedure will be documented by filming/taking photo during this part of the surgery. After surgery, the surgeon will document in the medical records and mark with a pen on a print-out of the injection map where the actual injections were placed. 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.

4.3 Follow-up period

4.3.1 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.

4.3.2 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. If the 15O PET is not available at the hospital where the patient is enrolled, the patient will be referred to another hospital for this assessment only; however, the CT scan may also be performed at the site of the 15O PET scan if required.

Before the 15O PET assessment it should be verified that the patient does not have:

- Heart rate < 40 bpm (ECG verified)
- Systolic blood pressure < 90 mmHg

For other assessments, refer to Table 2.

4.3.3 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. If the 15O PET is not available at the hospital where the patient is enrolled, the patient will be referred to another hospital for this assessment only; however the CT scan may also be performed at the site of the 15O PET scan if required.

4.3.4 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.

Before the stress echocardiography/LAD CFVR assessment it should be verified that the [redacted]

- [redacted]
- [redacted]

Any mobile phone that has been provided to the patient for d6MWT and MCWS will be returned.

For other assessments, refer to Table 2, Section 4 .

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms (eCRF) as specified in the Clinical Study Protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments (NA)

Efficacy is only evaluated in an exploratory fashion is this study.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in Table 1 and Table 2, Section 4.

The clinical chemistry, haematology and urinalysis 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. AstraZeneca will provide the same type of urine dipstick test kit to all sites.

The laboratory variables given in Table 3 and Table 4 below will be measured.

Table 3 Standard Clinical Laboratory Evaluation Panels

Hematology/Hemostasis (whole blood)	Clinical Chemistry* (serum or plasma)
White blood cell (WBC) count	Sodium
Red blood cell (RBC) count	Potassium
Hemoglobin (Hb)	Urea
Hematocrit (HCT)	Creatinine
Mean corpuscular volume (MCV)	Albumin
Mean corpuscular hemoglobin (MCH)	Calcium
Mean corpuscular hemoglobin concentration (MCHC)	Phosphate
Neutrophils absolute count	Alkaline phosphatase (ALP) "LIVER PANEL"
Lymphocytes absolute count	Alanine aminotransferase (ALT) "LIVER PANEL"
Monocytes absolute count	Aspartate aminotransferase (AST) "LIVER PANEL"
Eosinophils absolute count	Total bilirubin "LIVER PANEL"
Basophils absolute count	FSH (females only, at screening)
Platelets	LH (females only, at screening)
Reticulocytes absolute count	**Urinalysis**
Coagulation	Glucose (dipstick)
International normalized ratio (INR)	Albumine (quantification/semi-quantification)
Activated partial thrombin time (APTT)	Protein (dipstick)
Fibrinogen	Blood (dipstick)
	WBC (leukocytes) (dipstick)
	Creatinine (quantification)

Table 4 Other Clinical Safety Panels

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

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.2 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).

For handling of AEs based on examinations and tests see Section 6.3.6

5.2.3 ECG

12-lead ECG recordings will be collected using provided ECG machines according to the assessments schedule, see Table 1 and Table 2, Section 4 using. 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. Digital ECGs in Table 1 and Table 2 refers to the storage of digital Safety ECG source files that are retrievable for adjudication if required, e.g. for off-line analysis by experienced ECG readers.

Abnormal values shall not be recorded as AEs unless deemed clinically significant. The printout of the ECG is to be signed, dated and filed in the ISF along with a signed and dated copy (if the printouts are not on archive-quality paper).

To ensure robust data to evaluate and confirm potential outliers in the coming increased cardiovascular risk population, the requirement is to use digitally stored 12-lead Safety ECGs where the digital source file is available for analysis. Telemetry online ECG surveillance for rhythm monitoring and arrhythmia detection will be done at the given time points. Telemetry will be initiated the day before operation when the patient arrives to the hospital ward and continue until the patient is moved to the operating room (interruptions may be necessary for clinical routines and other study assessments). That will provide collection of some pre-

operative baseline rhythm and heart rate monitoring (preferably at least 6 hours of total duration of pre-operative telemetry but will depend on clinical routines). It will then be re-started when the patient comes back to the ward after the operation and continue as long as the patient stays at the ward (approximately 4 days post-operatively). Arrhythmia episodes will be visually confirmed by the attending physician and printed and if possible stored digitally for potential over read by cardiologist. If site has the capability to store telemetry data digitally, this should be done.

The following parameters or time intervals will be recorded for each ECG: RR, PR, QRS, QT, QTcF and heart rate (HR). A summary of clinically relevant ECG findings from 12-lead ECGs and observed arrhythmias during telemetry will be presented and discussed at the SRB/SRC meetings (see Section 3.11.1)

5.2.4 Vital signs

Vital signs will include pulse, and systolic and diastolic blood pressure. Vital signs will be obtained at time points indicated in Table 1 (and ad- hoc as medically indicated).

For handling of AEs based on examinations and tests see Section 6.3.6

5.2.4.1 Pulse, pulse oximetry and blood pressure

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.

Measurements will be done at the time points indicated in see Table 1 and Table 2, Section 4.

5.2.5 Other safety assessments

5.2.5.1 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 3 or 4 post CABG.

5.3 Other assessments

A number of exploratory assessments will be performed in the study as described below.

5.3.1 15O PET and CT angiogram

Prior to CABG, each patient will undergo a dynamic oxygen-15 labelled water positron emission tomography (15O PET)/CT scan, which generates a combined image of coronary angiogram superimposed on a myocardial perfusion map to locate areas of myocardial ischemia and dysfunction.

If the 15O PET is not available at the hospital where the patient is enrolled, the patient will be referred to another hospital for this assessment only. For any site where this arrangement is applicable, it will be clearly stated in ICF that the patient will have to perform the PET assessments in another, named hospital. The CT scan may also be performed at the site of the 15O PET scan if required.

As explorative efficacy readouts, global and regional myocardial perfusion and wall motion will be studied by 15O PET and echocardiography, respectively at 1 and 3 months post CABG.

5.3.2 Echocardiography

Comprehensive echocardiographic examination will be performed with patients in the left recumbent position at rest. Standard clinical cardiac transducers will be used for B-mode, colour Doppler, and tissue Doppler imaging. CINE-loops[1] of the parasternal long- and short-axis views, apical 4-, 2-, and 3-chamber views, and subcostal views will be obtained and stored for off-line analysis of cardiac structure and function, as detailed in the MoP for Echocardiography (detailed echocardiography protocol) that will be supplied to all study sites. Doppler and tissue Doppler echocardiography will be performed to obtain indices necessary for comprehensive assessment of left ventricular (LV) diastolic function and non-invasive hemodynamic measurements, as detailed in MoP. All echocardiographic data will be submitted to a central core lab for analysis.

[1] A CINE-loop is a period of images, stored digitally as a sequence of individual frames.

[redacted]

5.3.3 Gyrocardiography

For practical and logistical reasons, the exploratory assessment gyrocardiography will not be performed in this study.

5.3.4 Clinical Outcome Assessments

Two (Patient Reported Outcomes) PRO questionnaires will be used to address symptoms and impact of coronary disease and they will be evaluated as exploratory objectives.

The PROs in the study are: Kansas City Cardiomyopathy Questionnaire (KCCQ) and Seattle Angina Questionnaire (SAQ).

The PRO questionnaires used in this study will all be collected by paper, subject-self completed and do not require training. Site personnel or designated data management staff should enter the responses in the appropriate sections of the Case Report Form. The total time estimated to complete the questionnaires at the clinic visit is approximately 20 min. The questionnaires to be used are further described in Section 5.3.4.1 and 5.3.4.2.

The time points for the below listed PRO assessments are given in Table 1 and Table 2, Section 4.

PRO questionnaires should be completed by the patient in private. Appointed site staff should remind patients that there are no right or wrong answers and avoid clarifying items in order to avoid bias.

Patients must not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (e.g., spectacles or contact lenses) for reading and does not have them when he attends the clinic, the patient will be exempted from completing the PROs.

The patient should be given sufficient time to complete the PRO questionnaires at his/her own speed. Appointed site staff must monitor compliance to ensure all data is captured.

5.3.4.1 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.

The master version is enclosed in Appendix D.

5.3.4.2 Seattle Angina Questionnaire

The Seattle Angina Questionnaire is a sensitive, specific, and responsive health-related quality of life instrument for coronary artery disease.

The SAQ is 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).

The master version is enclosed in Appendix E.

5.3.5 NYHA classification

Classification of heart failure symptoms will be done according to New York Heart Association (NYHA) at the time points given in Table 1 and Table 2, Section 4.

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

The digital 6-minute walk test (d6MWT) and the "Maximum Continuously Walked Steps" (MCWS) are non-invasive measures of mobility. It is optional for the patient to participate in this exploratory assessment. This will not be applicable in Germany any other additional country joining the study.

At Visit 2, patients will be invited to participate in the optional AZ Activity App component of the study. During this visit patients will be provided with a mobile phone (unless they have a suitable iPhone already) and given access to a mobile software application (app) that will be used to conduct the d6MWT and MCWS. The app will be activated on-site at visit 2 and a supervised d6MWT will take place. Follow up and a supervised d6MWT will take place at all the subsequent physical visits to the site (except visit 3) as outlined in Table 1 and Table 2. The timepoint of supervised d6MWT will be collected in the eCRF to be able to distinguish between supervised and unsupervised d6MWT. There will also be automated reminders to encourage the patient to regularly perform an unsupervised d6MWT at home from visit 2 and onwards. In addition, continuous measurement of MCWS will take place passively as the patient carries the phone around, which should be done as much as possible until visit 7.

Soon after visit 2 an automated reminder will be sent out. The first d6MWT test after visit 2 if conducted prior to dosing will be the ‘at-home baseline’.

[redacted]

5.4 Pharmacokinetics

Pharmacokinetics for AZD8601 will not be assessed as part of the study since no drug levels are expected in plasma. Plasma samples will be collected and stored for potential assessment of plasma AZD8601 levels. Any results will be presented outside of this CSR. For time points see Table 1 and Table 2, Section 4 and Section 5.7

5.5 Pharmacodynamics

For samples taken for analysis of exploratory biomarkers, see Section 5.7. No other pharmacodynamics (PD) samples will be taken.

5.6 Genetics

In this study, no genetics samples will be collected.

5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory to be able to participate in the study.

Biological samples (e.g., blood samples) will be collected for analysis of exploratory biomarkers to assess correlations with disease activity, effects of AZD8601, clinical outcomes and toxicity. This includes VEGF-A downstream biomarkers. As outlined in Table 5, some exploratory biomarkers will be analysed and reported within this study and others may potentially be analysed. For exploratory biomarkers that might be analysed, results will be presented outside the CSR. Samples will be collected at the visits and time points listed in Table 1 and Table 2. 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 5 Exploratory biomarkers

Panel Name	Biomarkers	Analyses
Cardiovascular biomarkers	[redacted] (change from baseline 6 months post CABG)	Analysis will be performed as part of the study and done at a local laboratory at or near to the Investigator site. Sample tubes and sample volumes may vary depending on laboratory method used and routine practice at the site.
VEGF-A protein	Venous blood samples for the determination of plasma concentrations of VEGF-A protein	Analysis will be performed as part of the study. 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. Samples will be collected at the time points given in Table 1 and Table 2 Section 4.
Potential exploratory analysis of plasma concentrations of AZD8601 (VEGF-A modRNA)	Samples will be collected for potential future analysis	Any data from these potential analyses will be presented outside the CSR.
Potential exploratory biomarker research	Samples will be collected for potential exploratory research aimed at investigating biomarkers including VEGF-A downstream biomarkers involved in PK, PD, efficacy, safety and tolerability related to AZD8601 treatment	Samples to be handled by a central laboratory will be collected, labelled stored and shipped as detailed in the Laboratory Manual. Plasma samples will potentially be analysed for VEGF-A concentrations, by a qualified vendor on

Panel Name	Biomarkers	Analyses
Potential Analysis of Anti-drug Immunogenicity	Samples for potential analysis of anti-drug immunogenicity will be collected.	behalf of AstraZeneca Research and Development (R&D), using an assay that has been validated to fit the exploratory purpose of the study. Samples will be collected at the time points given in Table 1 and Table 2 Section 4.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest (i.e. VEGF-A) at the time of receipt by the analytical laboratory will be analysed.

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.7.3 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca designated Biobank during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

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

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

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

- Results in death

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from Visit 3 (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).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at Visit 6 in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Causality assessment to drug injection procedure
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

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

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

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated variables should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1**

calendar day of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

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

6.5 Overdose

An overdose is defined as a patient receiving a dose of AZD8601 in excess of that specified in this protocol. No specific treatment is recommended for an overdose. The Investigator will use clinical judgement to treat any overdose.

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

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

- If the pregnancy is discovered before the study patient has received any study drug

6.6.1 Maternal exposure

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. The pregnancy shall be reported to AstraZeneca.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

In case of pregnancy, the pregnancy data and the outcome of the pregnancy will be collected.

6.6.2 Paternal exposure

As a precaution, all male patients should avoid fathering a child by either true abstinence or the use of two effective means of contraception with their partner from the time of IP administration until 3 months after the last dose of IP. Should a partner, despite precautions, become pregnant during this period it should be reported in the same manner as described in Section 6.6.1 if the partner consents to this.

Sperm donation

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

6.7 Medication Error

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

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognize that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

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

- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Study governance and oversight

Safety of the patients in this clinical trial is closely monitored on an on-going basis by AstraZeneca representatives including the study physician. After each sentinel cohort the SRB will review 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. In parallel an unblinded study independent SRC will review the same data as described in Section 3.11.13.11.1.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 6 Investigational products

Investigational product	Dosage form and strength	Manufacturer
AZD8601	AZD8601 solution for injection [redacted]	AstraZeneca
AZD8601	AZD8601 solution for injection [redacted]	AstraZeneca
Placebo	Placebo for AZD8601 solution for injection	AstraZeneca

The manufacturing, labelling, packaging and release of AZD8601 and placebo will be conducted following Good Manufacturing Practise (GMP) by AstraZeneca. AZD8601 and matching placebo will be supplied in glass vials and labelled with a multi-language label.

Prior to dosing, an unblinded pharmacy personnel will prepare patient specific dosing syringes. The study drug will be handled according to the Handling Instruction.

7.2 Dose and treatment regimens

At Visit 3 patients will receive either AZD8601 or placebo. AZD8601 will be administered as epicardial injections. Thirty (30) injection [redacted]

Placebo for AZD8601 will be administered in the same manner as AZD8601 and in a volume to match AZD8601.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the vials specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to the patient.

Study site staff will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction should be signed.

7.7 Concomitant and other treatments

The concomitant medications not allowed at entry and/or during the study are listed below.

Table 7 Prohibited medication

Prohibited Medication/Class of drug:	
Persantin or Asasantin. Dipyridamole, Theophyllamine or Fluvoxamine	Ongoing treatment at entry and during the study

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- Refer to Statistical Analysis Plan (SAP) for details

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to the first patient in to the study. Any subsequent amendments to the SAP will be documented, with final amendments completed prior to unblinding of the data for the analysis. Details of all analysis will be fully documented in the SAP.

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed.

8.2 Sample size estimate

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 randomized and receive treatment in order to achieve 21 evaluable patients (7 per arm).

8.3 Definitions of analysis sets

8.3.1 Safety analysis set

The safety analysis set will include all randomized patients who received at least one injection of IP. Patients will be analysed according to the treatment which they actually received. Any major deviations from randomized treatment will be listed and considered when interpreting the safety data.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses.

8.3.2 Exploratory analysis set

The exploratory analysis set will consist of all randomized patients 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.

The available exploratory data of patients excluded from the exploratory analysis set will be listed only.

8.3.3 All Enrolled Patients

All enrolled patients will include patients who have signed the informed consent form. Patients will be analysed according to the treatment to which they were randomized.

8.3.4 All Randomized Patients

All randomized patients will include patients who were randomized. Patients will be analysed according to the treatment to which they were randomized.

8.4 Outcome measures for analyses

8.4.1 Safety variables

The primary outcome measures are safety and tolerability variables. They are listed below and in Section 5.2. This includes:

- Adverse events
- Vital signs (blood pressure, pulse, pulse oximetry)
- ECG
- Physical examination
- Laboratory assessments (hematology, clinical chemistry and urinalysis). See Table 2 and Table 3, Section 5.2.1
- Hemopericardium and/or tamponade assessment, and LVEF with echocardiography
- Coagulation and use of concomitant medication

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

8.4.2 Exploratory variables

- 15O PET parameters. The output variables, measured at baseline (pre CABG), 1 and 3 months post CABG, will be
  - Regional sMBF in the myocardial region that received injections
  - Global sMBF
  - Regional MPR in the myocardial region that received injections
  - Global MPR
- Echocardiography parameters. The output variables, measured at baseline (pre CABG), 1, 3 and 6 months post CABG, will be
  - Regional wall motion (speckle tracking/vector velocity derived strain) 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 and LVESV) or LVEF. Measured at baseline (pre CABG), 1, 3 and 6 months post CABG.
  - [redacted]

- Clinical symptoms. The output variables, measured at baseline (pre CABG), 1, 3 and 6 months post CABG, will be
  - KCCQ
  - NYHA class
  - Seattle Angina Questionnaire
- Walking tests. The output variables will be
  - digital 6-min walk test (d6MWT). Defined as the distance walked by patients during a six-minute period.
  - maximum continuous walked steps (MCWS). Defined as the maximum number of steps the patient has walked without stopping for a defined time.

8.4.3 Exploratory biomarkers

The exploratory research biomarkers are listed below and in Table 5. They include:

- Cardiovascular biomarkers. The output variables, measured at baseline (pre CABG) and 6 months post CABG, will be
  - hsTnT
  - NT-proBNP
- Plasma VEGF-A concentrations. Both treated and placebo samples will be analysed for VEGF-A protein, using qualified assays. The output variables will be
  - Plasma concentration at visit 2 (geometric mean of two measurements)
  - Change from baseline (visit 2) to 1 month post-dosing
  - Plasma concentration at visit 5

- Plasma concentration at visit 3 pre-surgery
- AUC 0-72 hours post dosing

8.5 Methods for statistical analyses

Placebo data will be pooled throughout.

Demographic and baseline data will be summarized by treatment and overall.

All statistical analyses and production of tables, figures and listings will be performed using SAS version 9.2 or later.

If not otherwise specified, baseline refers to the last measurement prior to IP administration.

8.5.1 Analysis of the primary variable (s)

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

All safety variables will be summarised by treatment group and visit using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous data and absolute and relative frequencies for categorical data).

AEs will be summarised by treatment group, treatment related and severity by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT).

Laboratory data for haematology and clinical chemistry will be summarized by treatment group and visit. The number and percentages of patients with haematology and clinical chemistry treatment emergent laboratory of changes with respect to normal ranges between baseline and post treatment will be tabulated. The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarised by treatment group. Categorical outliers may be presented by numbers but need to be considered in context of inclusion/exclusion criteria. Physical examination and vital signs variables will be summarised by treatment group.

Unless otherwise stated, the following rules will apply to any repeated safety assessments:

- If the repeated measurement of a specific parameter occurs prior to IP administration (Day 1), the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline.

8.5.2 Exploratory analysis

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

All exploratory variables will be summarised by treatment group and visit using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum and geometric mean and geometric SD if applicable for continuous data and absolute and relative frequencies for categorical data). P-values will be unadjusted and tests will be two-sided.

Mean values per treatment will be plotted against visit.

Geometric mean per treatment and individual plasma levels of VEGF-A will be plotted against time after dosing. Calculation of VEGF AUC - Area under the concentration-time curve (µmol*h/L)- will be done by linear up/ log down trapezoidal summation.

Change from baseline will be analysed for all exploratory variables with baseline and post-dose measurements. Change from baseline for some exploratory variables will be analysed using Analysis of Covariance, (with treatment as fixed effect, patient as random effect and baseline value as covariates) or a repeated measurements model (with treatment, visit and treatment-by-visit interaction as fixed effects, baseline as covariate and patient as random effect). If an approximation of the variable of interest follows a log-normal distribution rather than a normal distribution, a logarithmic transformation of the variable of interest will be done. All variables that are transformed will be back transformed for reporting.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD8601.

9.4 Data management

Data Management will be performed by a data management vendor per the Data Management Plan (DMP).

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Data Management Vendor.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

Where necessary SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory (ies) internal or external to AstraZeneca.

Management of external data

The data management vendor will receive and manage all external data according to the DMP.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The patients potentially eligible for this study, as assessed by the review of Inclusion and Exclusion criteria, will be given written and oral information about the study and will be asked to sign the ICF for inclusion in the study. The main ICF will include consent for biological sampling and for storage of biological samples for future research.

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee are to approve the revised ICF before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

Cohn JN et al 1993
Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 1993;87:VI-5–VI-16

The CONSENSUS Trial Study Group 1987
The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe CHF: results of CONSENSUS. N Eng J Med 1987;316: 1429–1435

Dib N et al. 2011
Dib N, Khawaja H, Varner S, McCarthy M, Campbell A. Cell Therapy for Cardiovascular Disease: A Comparison of Methods of Delivery. J. of Cardiovasc. Trans. Res. 2011; 4:177–181

Djousse L et al. 2009
Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA 2009;302:394-400.

Ferrara N et al. 1991
Ferrara, N., Houck, K. A., Jakeman, L. B., Winer, J. and Leung, D. W. The vascular endothelial growth factor family of polypeptides. J. Cell. Biochem. 1991; 47: 211–218.

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016
GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545–602

GBD 2015 Mortality and Causes of Death Collaborators 2015
Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 2016; 388: 1459–544

Go AS et al. 2013
Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino

ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics–2013 update: A report from the American Heart Association. Circulation 2013;127:e6-245.

Karatolios et al. 2012
Karatolios K, Pankuweit S, Moosdorf RG, Maisch B. Vascular Endothelial Growth Factor in Malignant and Benign Pericardial Effusion Clin. Cardiol. 2012; 35:377–381

Mathiasen A et al. 2015
Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Fischer-Nielsen A, Kofoed KF, Haack-Sørensen M, Ekblond A, Kastrup JBone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial) European Heart Journal. 2015;36, 1744–1753

Hedman et al. 2009
Hedman M, Muona K, Hedman A, Kivelä A, Syvänne M, Eränen J, Rantala A, Stjernvall J, Nieminen MS, Hartikainen J, Ylä-Herttuala S. Eight-year safety follow up of coronary artery disease patients after local intracoronary VEGF gene transfer. Gene Ther 2009;16:629–634.

Medical Advisory Secretariat 2010
Medical Advisory Secretariat. Positron emission tomography (PET) for the assessment of myocardial viability: an evidence-based analysis. Ont Health Technol Assess Ser. 2010; 10(16) 1-80.

Muona K et al. 2012
Muona K, Mäkinen K, Hedman M, Manninen H, Ylä-Herttuala S. 10-year safety follow-up in patients with local VEGF gene transfer to ischemic lower limb. Gene Ther 2012;19:392–395.

Packer M et al. 1996
Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH.The effects of carvedilol on morbidity and mortality in patients with chronic heart failure. N Eng J Med 1996;334:1349–55

Parameshwar J et al. 1997
Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe heart failure. Am Heart J 1992;123:421–6.

Pitt B et al. 1997
Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure. (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747–752.

Rahimtoola SH 1985
Rahimtoola SH. A perspective on the three large multicentre randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985; 72(Suppl. 5), 123–135

Rahimtoola SH 1989
Rahimtoola SH. The hibernating myocardium. Am. Heart J. 1989; 117, 211–221

Rosamond W et al. 2007
Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". Circulation. 115 (5): e69–171

Rosengart TK et al. 2013
Rosengart TK, Bishawi MM, Halbreiner MS, Halbreiner MS, Fakhoury M, Finnin E, Hollmann C, Shroyer AL, Crystal RG. Long-term follow-up of a phase 1 trial of angiogenic gene therapy using direct intramyocardial administration of an adenoviral vector expressing the VEGF121 cDNA for the treatment of diffuse coronary artery disease. Hum Gene Ther 2013;24:203–208.

Saraste A et el. 2017
Saraste A, Knuuti J. PET imaging in heart failure: the role of new tracersHeart Fail Rev. 2017; 22(4):501-511

Stirrup J et al. 2017
Stirrup J, Velasco A, Hage FG, Reyes E,Comparison of ESC and ACC/AHA guidelines for myocardial revascularization. J Nucl Cardiol. 2017; 24(3): 1046–1053.

Task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology 2001
Task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology: Remme WJ, Swedberg K (cochairmen). Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–1560.

Yancy CW et al. 2013
Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WWH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. 2013;128:e240-e327

Zangi L et al. 2013
Zangi L, Lui KO, von Gise A, Ma Q, Ebina W, Ptaszek LM, Später D, Xu H, Tabebordbar M, Gorbatov R, Sena B, Nahrendorf M, Briscoe DM, Li RA, Wagers AJ, Rossi DJ, Pu WT, Chien KR. Modified mRNA directs the fate of heart progenitor cells and induces vascular regeneration after myocardial infarction. Nature Biotechnology. 2013; 31,898–907

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

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

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

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

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

1. Introduction

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

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

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

2. Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

3. Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. Follow-up

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition.

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.

- Subsequent to this contact the Investigator will:

  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long, as medically indicated. Complete follow-up SAE Form as required.

  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.

  - Complete the three Liver CRF Modules as information becomes available.

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL

elevations other than the IMP:

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

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

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

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDAGuidanceforIndustry(issuedJuly2009)'Drug-inducedliverinjury:Premarketing clinicalevaluation'

Appendix D Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

Study ID# ☐☐☐☐☐

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

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

Please place an ☒ in one box on each line

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

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

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

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

Study ID# ☐☐☐☐☐

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

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

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

It has been...

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

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

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

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

It has been...

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

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

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

Study ID# ☐☐☐☐☐

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

It has been...

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

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

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

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

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

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

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

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

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

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

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

Study ID# ☐☐☐☐☐

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

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

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

Please place an ☒ in one box on each line

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

Appendix E Seattle Angina Questionnaire

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina** **over the past 4 weeks**.

Activity	**Extremely Limited**	**Quite a bit Limited**	**Moderately Limited**	**Slightly Limited**	**Not at all Limited**	**Limited for other reasons or did not do the activity**
Dressing yourself	○	○	○	○	○	○
Walking indoors on level ground	○	○	○	○	○	○
Showering	○	○	○	○	○	○
Climbing a hill or a flight of stairs without stopping	○	○	○	○	○	○
Gardening, vacuuming, or carrying groceries	○	○	○	○	○	○
Walking more than a block at a brisk pace	○	○	○	○	○	○
Running or jogging	○	○	○	○	○	○
Lifting or moving heavy objects (e.g. furniture, children)	○	○	○	○	○	○
Participating in strenuous sports (e.g.swimming, tennis)	○	○	○	○	○	○

2. Compared with 4 weeks ago, how often do you have **chest pain, chest tightness, or angina** when doing your **most strenuous** activities?

I have had **chest pain, chest tightness, or angina...**

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
○	○	○	○	○	○

3. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness, or angina**?

I have had **chest pain, chest tightness, or angina...**

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
○	○	○	○	○	○

4. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness, or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
○	○	○	○	○	○

5. How bothersome is it for you to take your pills for **chest pain, chest tightness, or angina** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
○	○	○	○	○	○

6. How satisfied are you that everything possible is being done to treat your **chest pain, chest tightness, or angina**?

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

7. How satisfied are you with the explanations your doctor has given you about your **chest pain, chest tightness, or angina**?

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

8. Overall, how satisfied are you with the current treatment of your **chest pain, chest tightness, or angina**?

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

9. Over the past 4 weeks, how much has your **chest pain, chest tightness, or angina** limited your enjoyment of life?

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

10. If you had to spend the rest of your life with your **chest pain, chest tightness, or angina** the way it is right now, how would you feel about this?

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

11. How often do you think or worry that you may have a heart attack or die suddenly?

I can't stop thinking or worrying about it	**I often** think or worry about it	**I occasionally** think or worry about it	**I rarely** think or worry about it	**I never** think or worry about it
○	○	○	○	○

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d9150c00003-csp-v5		
Document Title:	D9150C00003 Clinical Study Protocol version 5	
Document ID:	Doc ID-003605986	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
04-Mar-2020 09:55 UTC	[redacted]	Content Approval
03-Mar-2020 12:09 UTC	[redacted]	Content Approval
03-Mar-2020 11:15 UTC	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.