Clinical Study Protocol	
Drug Substance	AZD5718
Study Code	D7550C00003
Version	Version 5.0
Date	11 February 2019

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 5.0 dated 11 February 2019 Changes to the clinical study protocol are summarized below
Substantial amendment to the protocol: The estimated date of last patient completed has been changed from Q2 2019 to Q1 2020. The reason behind is slower recruitment than anticipated. This is reflected in the Clinical Study Protocol Synopsis, Study Period Section. **Non-substantial amendment to the protocol:** The time window for visit 4 (4 weeks) and visit 4c (12 weeks) has been increased from ±2 days to ±3 days, in order to facilitate the flexibility of visit planning. Figure 1 and Table 1 have been updated to reflect this change. Appendix D wording has been updated in order to clarify the process of Potential Hy's Law and Hy's Law cases reporting in accordance with the FDA Guidance for Industry (issued July 2009) 'Drug induced liver injury: Premarketing clinical evaluation'."

Version 4.0 dated 5 September 2018 Changes to the clinical study protocol are summarized below
Non-substantial amendment to the protocol: 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, in order 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. Section 5.2.1 Laboratory safety assessment, Table 2, and Section 8.5.3 have been updated accordingly.

Version: 3.0 dated 11 April 2018

Changes to the clinical study protocol are summarized below
Substantial amendments to the protocol: **Treatment extension and Study Objectives** The treatment period has been extended from 4 weeks to 12 weeks. The extended treatment period includes 2 new visits; an 8-week Visit (Visit 4b) and a 12-week visit (Visit 4c). With the intention of further development of AZD5718 as a chronic treatment for the secondary prevention in high-risk CV patients, the aim is to evaluate the effects of inhibition of the 5-LO pathway mediated inflammation as well as physiological consequence and safety profile in a longer term, i.e. reasonably beyond the initial short-time treatment period of 4 weeks. Therefore, treatment prolonged up to 12 weeks will allow to achieve and to assess sustained inhibition of leukotriene-mediated inflammation (urine-LTE_4 and blood-LTB_4) following the initial decrease after 4 weeks treatment. In addition, treatment with AZD5718 prolonged up to 12 weeks will allow to assess sustained dynamics, gradual and steady improvement of myocardial microvascular function (coronary flow reserve and echocardiography parameters) in post-ACS patients on top of the long-term Standard of Care. Extended up to 12 weeks treatment period will provide with more complete AZD5718 safety and tolerability profile with longer treatment exposure, on top of long-term Standard of Care in post ACS patients with CAD and support further clinical development. Since some patients have already been randomized to the study, they will have a treatment period of 4 weeks, while future randomized patients will have a treatment period of 12 weeks. The main endpoint, u-LTE_4, remains the same. Two new secondary endpoints are added: u-LTE_4 at 12 weeks and CFVR at 12 weeks. The following sections of the clinical study protocol (CSP) have been updated to reflect this change: Section 1.2 (Rationale for study design, doses and control groups), Section 1.3 (Benefit/risk and ethical assessment), Section 1.4 (Study Design including Figure 1), Section 2 (Study objectives) and Section 4.1 (Study Procedures including Table 1), Section 7.2 (Dose and treatment regimens) and Section 8 (statistical analyses). All text in the CSP mentioning the duration of the study have been updated accordingly, including the Study Title. **Increase in number of patients** The total number of patients that will be randomized in the study has been increased from 100 to approximately 138. The reason for increasing the total number of patients is to make sure that there are enough patients to evaluate the sustained effect on CFVR after 12 weeks, that is, about 33 evaluable patients per arm for AZD5718 [redacted] and placebo. An evaluable patient is defined as a patient with a valid CFVR measurement at Visit 2 (baseline), and one postbaseline visit as judged by the CFVR Core lab. The total number of patients for evaluation of uLTE4 and CFVR at week 4 will be more than 33 patients per high-dose and

placebo arm (exact number will be known at the unblinding at the end of the trail). This is due to the fact that patients that are already randomized to the study (approximately 38) will have a treatment period of 4 weeks while future randomized patients (approximately 100) will have a treatment period of 12 weeks.
Section 1.4 (Study Design) has been updated to reflect this change, however, the updated numbers are reflected in all relevant sections of the CSP.

Interim analysis
The interim analysis is updated as follows: The text is revised to alter the futility interim analysis to two administrative interim analyses for internal decision making. The futility analysis has been removed to be able to evaluate the sustained effect on u-LTE_4 at 12 weeks. The focus of the study extended to 12 weeks aiming on evaluation 5-LO pathway inhibition, ie not only at the end of 4 weeks but at the end of 12 weeks to ensure the use of the drug in a chronic setting. The futility analysis has therefore been changed into two administrative interim analyses for internal decision making. In the event of positive outcome at any of the administrative interim analyses an evaluation of exposure-response relationship may be performed. This is reflected in the Study Synopsis (Statistical methods) and Section 8.5.6 (Interim analysis).

Biomarker sampling
An additional biomarker sample will be collected at day 2 after the ACS.
The rationale for adding a day 2 sample is to be able to model the kinetics of inflammatory biomarkers post ACS. A minimum of three samples from each patient (ideally before and after the peak expression) is required for mathematical modelling. Individual differences between the patients are expected. Therefore, several samples from the same patient are required. Since, the peak expression is expected to take place at around day 1-3 post ACS, namely this timeframe is the most crucial for the biomarker kinetics and therefore a day 2 sample has been added.
The following sections have been updated to reflect this change: Section 1.4 (Study Design) and Section 4.1(Study Procedures Visit 1 as well as Table 1).

Safety sampling
TSH, free T3, free T4 and total T4 has been added to the safety laboratory assessments at Visit 2 (Baseline at Randomization), Visit 4 (4 weeks), Visit 4c (12 weeks) and Visit 5 (Follow-up). This decision is based on a recently completed 3 months toxicity study in rats. In rats, though not in dogs, treatment with AZD5718 in doses of QD 1000 mg/kg/day (> 200 folds higher than clinical exposure) caused minimal follicular cell hypertrophy in the thyroid gland which is considered as adaptive rather than adverse and based upon experience, most likely reversible. This risk is not anticipated in humans, however repeated safety assessment of thyroid functions will be performed in study subjects.
This is reflected in the List of abbreviations and definition of terms, Section 1.3

(Benefit/risk and ethical assessment), Section 4.1(Study Procedures including Table 1) and Section 5.2.1(Laboratory safety assessments including Table 2).

Non-substantial amendments to the protocol:

Section 5.3.1(Other research biomarker assessments): ApoB will be analysed instead of ApoB100. The reason behind the change is that local labs do not have the possibility to analyse ApoB100, as originally planned, only ApoB. The change applies to all sections mentioning ApoB100.

Section 6.4 (Reporting of serious adverse events): The text was revised to say that "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" instead of by phone as originally stated. This was revised based on a study team decision in order to be in line with normal reporting routines.

Section 8.3.2 (Safety analysis set): "Major deviation" has been replaced by "important protocol deviation".

Section 8.4.1 (Efficacy variables):
Corrected text to state that LV Global Circumferential Strain (GCS) is only to be recorded at rest and not at hyperaemia.

In addition, minor edits in terms of spelling, lay-out and clarifications have been made throughout the document.

Version: 2.0 dated 10 January 2018

Changes to the protocol are summarized below

Section 2.4 (Exploratory objectives): the exploratory objective related to gyrocardiography was removed, based on a decision by the project team. Consequently, all text in the CSP where gyrocardiography measurement is described was removed: Section 4.1 (Visits 2, 4 and 5 and Table 1), Section 5.1.5 and Section 8.4.3.

Section 3.2 (Exclusion criteria):
Criterion no 13 was updated as follows:
"NYHA class III-IV heart failure **or decompensated heart failure** at discharge or hospitalization for exacerbation of chronic heart failure within the previous 3 months from

ACS “
This was added based on a request by the Swedish MPA.

Criterion no 16 was updated as follows:
“Known allergy to adenosine **and mannitol, or experience of previous adverse effects of adenosine stress testing.”**
This was added based on a request by the Swedish MPA.

Criterion no 26 was clarified as follows:
“Participation in another **interventional** clinical study with an investigational **pharmaceutical** product during the last 3 months **also including drug eluting stents**
This was clarified based on a project team decision.

Section 3.4 (Procedures for handling incorrectly enrolled or randomized patients): The section was revised to say that when a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the patient must discontinue the treatment and be withdrawn from the study.
The revision is based on a request from the Swedish MPA.

Section 4.1 (Study Procedures):
Corrected text for Visit 2 by removing incorrect text about CFVR measurement at screening (inconsistent with Table 1).
Corrected text for Visit 5 by removing incorrect text about PRO questionnaire (inconsistent with Table 1).

Section 8.4.4(Exploratory biomarkers): Removed GDF15, IL-1B and IL-6 from the list of exploratory biomarkers to be summarized statistically in the CSR, instead they will be referred to in an exploratory SAP and reported separately. This is based on a decision by the project team.

Version: 1.0 dated 5 July 2017
Initial creation

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

International Co-ordinating Investigator:

[redacted]

Study site(s) and number of subjects planned

This study will be a multi-centre study conducted at approximately 10 centres in 3 countries. Approximately one hundred and thirty-eight (138 patients with coronary artery disease (CAD) will be randomized to ensure at least 66 evaluable patients receiving 12 weeks treatment with AZD5718 [redacted] or placebo. About 20% of the randomized patients will receive AZD5718 [redacted] The patients on lower dose are included to guide dose selection in future studies. The study was originally designed to be a 4-week study and was amended to be a 12-week study. Therefore, the total number of patients is greater than required for a 12 weeks study (about 100), this since some patients will only have 4 weeks of treatment.

Study period

Estimated date of first patient enrolled Q4 2017
Estimated date of last patient completed Q1 2020

Phase of development:

Phase IIa

Study design

Randomized, single-blind, placebo-controlled, parallel-group, multicentre study in patients with CAD.

NB. The study was originally designed to be a 4-week study and was amended to be a 12-week study. As a consequence, some patients will have a treatment period of 4 weeks only while others will have a treatment period of 12 weeks.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the pharmacodynamic (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 4 weeks in CAD patients.	Percentage change from baseline in levels of u-LTE_4 (see Section 8.4.1)

Secondary Objectives:	**Outcome Measures:**
• To assess the pharmacodynamics (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 12 weeks in CAD patients.	Percentage change from baseline in levels of u-LTE_4 (see Section 8.4.1)
• To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 12 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)
• To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 4 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)
• To assess the pharmacokinetics (PK) of AZD5718 after repeated oral dosing at 4 and 12 weeks in CAD patients	Standard model population pharmacokinetic (PK) parameters to be reported in a separate report.
• To assess the effect of AZD5718 on coronary flow parameters at 4 weeks in CAD patients	Change from baseline in: – LAD resting mean diastolic flow velocity – LAD hyperaemic flow velocity
• To assess the effect of AZD5718 on change in echocardiographic parameters at 4 weeks in CAD patients.	Change from baseline in: – Left Ventricular (LV) Ejection Fraction (LVEF) – LV global longitudinal strain (GLS) – LV global circumferential strain (GCS) – LV longitudinal early diastolic strain rate

Exploratory Objective:	Outcome Measures:
• To assess the effect of AZD5718 on coronary flow parameters at 12 weeks in CAD patients	Change from baseline in: – LAD resting mean diastolic flow velocity – LAD hyperaemic flow velocity
• To assess the effect of AZD5718 on change in echocardiographic parameters at 12 weeks in CAD patients.	Change from baseline in: – Left Ventricular (LV) Ejection Fraction (LVEF) – LV global longitudinal strain (GLS) – LV global circumferential strain (GCS) – LV longitudinal early diastolic strain rate

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

Target subject population

Male and female CAD patients aged 18-75, with BMI 18- 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 (ICF).

Duration of treatment

Eligible patients will be randomized in a ratio 2:1:2 to receive either AZD5718 [redacted]), AZD5718 [redacted] or Placebo. Treatment duration will be 12 weeks, once daily administration, to be taken with approximately 200 ml water in the morning with no restrictions on food intake.

Investigational product, dosage and mode of administration

Investigational product	Dosage form and strength	Dose	Manufacturer
AZD5718	[redacted] of AZD5718 [redacted] tablet	[redacted]	AstraZeneca
AZD5718	[redacted] of AZD5718 [redacted] tablet	[redacted]	AstraZeneca

Investigational product	Dosage form and strength	Dose	Manufacturer
Placebo to match (PTM) AZD5718 [redacted]	PTM AZD5718 [redacted] tablet	[redacted]	AstraZeneca
Placebo to match (PTM) AZD5718 [redacted]	PTM AZD5718 [redacted] tablet	[redacted]	AstraZeneca

Statistical methods

The primary efficacy and the first secondary variable will each test the null hypothesis that patients given AZD5718 [redacted] have less than 80% inhibition of u-LTE_4 compared to placebo, versus the alternative hypothesis that patients given AZD5718 [redacted] have equal or more than 80% inhibition of u-LTE_4 compared to placebo (one-sided 95% confidence interval).

The second and third secondary efficacy variable measuring change from baseline in CFVR will test the null hypothesis of no increase in CFVR in patients given AZD5718 [redacted] compared to placebo, versus the alternative hypothesis of an increase in CFVR in patients given AZD5718 [redacted] compared to placebo (one-sided 95% confidence interval).

The primary efficacy variable and the three first secondary efficacy variables measuring will be analysed using a repeated measurement model with treatment, type of Myocardial Infarction (MI) (STEMI vs NSTEMI) as factors and baseline value as covariate, with spatial power covariance structures (generalisation of an auto regressive covariance structure allowing for none-equidistant time points).

Efficacy variables will be analysed using the intention to treat (ITT) population. The randomization will be stratified with type of MI as a factor ST-elevation MI vs non-ST-elevation MI (STEMI vs NSTEMI).

Given anticipated effect size, 40 randomized patients on AZD5718 [redacted] and 40 randomized patients on placebo is needed accounting for non-evaluable patients to achieve an overall power of approximately 80% for the primary endpoint and secondary endpoints analysing change in CFVR. For dose selection in future studies, a treatment arm with patients receiving AZD5718 [redacted] is included in the study.

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

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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
AE	Adverse Event
ACS	Acute Coronary Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ApoA1	Apolipoprotein A1
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV-block	Atrioventricular block
bPWA	Brachial Pulse Wave Analysis
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CBFV	Coronary blood flow velocity
CCS	Canadian Cardiovascular Society grading of angina pectoris
cfPWV	Carotid-femoral Pulse Wave Velocity
CFVR	Coronary Flow Velocity Reserve
CKD	Chronic Kidney Disease
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
DAE	Discontinuation of Investigational Product due to Adverse Event
DCCT	Diabetes Control and Complications Trial
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EF	Ejection Fraction

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
5-LO	5-lipoxygenase
FLAP	5-lipoxygenase activating protein
Free T3	Free Triiodothyronine
Free T4	Free Thyroxine
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GDF15	Growth/differentiation factor 15
GLS	Global Circumferential Strain
GRACE	Global Registry of Acute Coronary Events
HbA1c	Haemoglobin A1c (glycated haemoglobin)
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HR	Heart Rate
hsCRP	High-sensitivity C-Reactive Protein
hsTnI	High-sensitive Troponin I
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFCC	International Federation of Clinical Chemistry
IL-1B	Interleukin 1 beta
IL-6	Interleukin 6
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.
INR	International normalized ratio
IP	Investigational Product
[redacted]	[redacted]
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation or special term	Explanation
LAD	Left Anterior Descending artery
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
Lp(a)	Lipoprotein a
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LSLV	Last Subject Last Visit
LIMS	Laboratory Information Management System
LTB_4	Leukotriene B4
LTE_4	Leukotriene E4
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MoP	Manual of Procedures
MPO	Myeloperoxidase
MPO mass	Myeloperoxidase protein level measurement
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-Terminal Prohormone of Brain Natriuretic Peptide
OAE	Other Significant Adverse Event
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
PT	Preferred Term
PTM	Placebo to Match
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMAD	Single and Multiple Ascending Dose

Abbreviation or special term	Explanation
SRC	Safety Review Committee
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TDE	Transthoracic Doppler Echocardiography
Total T4	Total Thyroxine
TSH	Thyroid Stimulating Hormone
u-	Urine
ULN	Upper Limit of Normal
WBC	White blood cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Cardiovascular diseases are leading causes of death globally, accounting for 17 million deaths, and for 39% of deaths in individuals under 70 years of age (WHO 2011). In United States alone 1.350.000 individuals suffer an acute coronary syndrome (ACS) annually (Lloyd-Jones D et al 2010). Atherothrombosis, i.e. the sudden rupture of an atherosclerotic plaque, is the principal cause of cardiovascular morbidity and mortality. Erosion and rupture of an atherosclerotic plaque leads to activation and aggregation of circulating platelets, resulting in the formation of a thrombi, which partially or totally occludes the coronary artery. However, while the clinical manifestations of plaque ruptures are the most prominent clinical signs of the disease, the whole atherosclerotic process in the arterial wall is characterized by lipid accumulation in the vessel wall thus forming the atherosclerotic plaques (Libby P 2013). Nevertheless another component of atherosclerosis and its subsequent clinical manifestations like ACS, is inflammation. Inflammation, in fact, is considered playing a critical role in plaque ruptures where it weakens the plaque's fibrous cap making it more prone for rupture. Secondly inflammation is a key component in event occurring after ACS. Besides the effect on plaque itself, post ACS myocardial damage and remodelling is essentially modulated by inflammation (Frangogiannis NG 2012).

Traditional cardiovascular pharmaceutical therapies, such as aspirin and statins, improve outcomes in patients with atherosclerotic cardiovascular disease. Patients with established coronary artery disease (CAD), especially with recent ACS however, still have residual cardiovascular risk even with these therapies. In the process of atherosclerosis, subsequent plaque rupture and eventual infarction area remodelling inflammation possesses a key role (Frangogiannis NG 2012). This is considered to be a consequence of various biochemical processes, including especially leukotrienes and its enzymatic regulator 5-Lipoxygenase (5-LO) (Spanbroek R et al 2003, Dwyer JH et al 2004, Bäck M 2008). During the reperfusion in ACS, leukocytes are activated and release a variety of oxidative stress response molecules and pro inflammatory lipid and peptide mediators (Funk CD 2005). Expression and activity of the 5-LO pathway has been linked to atherosclerotic plaque inflammation and progression (Qiu H et al 2006, Cipollone F at al 2005, van den Borne P et al 2014, Allen S at al 1998). In more detail, expression and activity of 5-LO pathway is elevated in unstable plaques (Qiu H et al 2006, Cipollone F at al 2005, van den Borne P et al 2014) and this has also been associated with vasoconstriction in atherosclerotic coronary arteries (Allen S at al 1998).

CAD can be divided to macrovascular and microvascular disease, both as different manifestations of atherosclerosis. Macrovascular CAD, i.e. obstructive CAD of epicardial coronary arteries has traditionally been the focus of CAD treatment (Montalescot G et al 2013). Microvascular circulation, on the other hand, consists of arterioles (diameter <100 μm) within myocardium and abnormalities in this arterial bed may also impair myocardial perfusion and result in ischaemia (Camici PG et al 2007). An indication of microvascular disease can be achieved with coronary flow velocity reserve (CFVR) which is an integrated measure of flow through both large epicardial arteries and coronary microcirculation (Camici PG et al 2015). Thus, an adequate assessment of microcirculation can be obtained when the

epicardial coronary arteries are free from significant stenosis (>50%). CFVR measurement is the ratio of resting coronary artery mean diastolic flow velocity in comparison to hyperaemic coronary artery mean diastolic flow velocity, where hyperaemia is often induced with pharmacologic agent such as adenosine infusion. CFVR of the left anterior descending (LAD) coronary artery during pharmacologic stress echocardiography has been found to provide effective prognostic information in patients with known or suspected CAD (Rigo F et al 2008). This seems evident across patient populations, such as those with diabetes or chronic kidney disease (Murthy VL et al 2012), or older age (Uren NG et al 1995). Particularly, a CFVR <2.0 has been associated with markedly increased cardiovascular (CV) risk in an unselected patient population (Rigo F et al 2008). However, cardiac microvascular function seems dynamic in nature as marked improvements in CFVR with pharmacotherapy have been induced within 8 weeks treatment (Tagliamonte E et al 2015). CFVR also reflects well both systolic and diastolic cardiac function consequently emphasizing the essential role of myocardial microvascular function in cardiac physiology (Blomster J et al 2016).

Several publications support the biological rationale and target validation for 5-LO-activating protein (FLAP) inhibitor in cardiovascular disease. Tardif et al. has shown that 5-LO Inhibitor VIA 2291 reduced *ex vivo* stimulated leukotriene B4 (LTB_4) production, non-calcified plaque volume and appearance of new coronary lesions in ACS patients. Moreover, VIA 2291 reduced plaque progression with treatment initiation 3 weeks after ACS (Tardif JC et al 2010). Additionally, human genetic associations that link FLAP and the 5-LO pathway to atherosclerotic cardiovascular disease (increased risk of myocardial infarction) have been made in Icelandic population (Helgadottir A et al 2004). Neutrophil adhesion in microvasculature can reduce coronary perfusion via FLAP-dependent mechanism whilst inhibition of FLAP pathway seems to improve microvascular function (Sala A et al 1993, Sala A et al 1996). Given the previous evidence from inhibition of this pathway it seems apparent that mechanism is involved in the processes of both macrovascular and microvascular CAD.

AZD5718, is a selective, reversible 5-lipoxygenase activating protein (FLAP) inhibitor which will attenuate production of pro-inflammatory and vasoactive leukotrienes by leukocytes e.g. neutrophils in the circulation encompassing both downstream cysteinyl leukotrienes measured as urine-leukotriene E4 (u-LTE_4) and leukotrienes measured as plasma LTB_4.

This Phase IIa Proof-of-Principle study will investigate if AZD5718, a FLAP inhibitor, can decrease u-LTE_4 levels and secondly if AZD5718 can improve CFVR as a measure of myocardial microvascular function. The study will also address safety and tolerability of AZD5718 on top of standard of care in CAD patients e.g. a post-ACS population. The result of the study will form the basis for the future clinical development programme for AZD5718 with the overall aim to investigate if AZD5718 can improve cardiovascular mortality and morbidity on top of standard of care in CAD patients.

1.2 Rationale for study design, doses and control groups

A randomized, blinded, parallel-group, multi-centre, placebo-controlled study design is standard in Proof-of-Principle studies and is considered the best design to achieve the objectives of the study, from both safety and efficacy perspectives. Overall, the study is

single-blinded regarding treatment strengths, but double-blinded in terms of active or placebo. This is due to the [redacted] and [redacted] tablets being of different size and number of tablets to digest differs between the treatment arms. To avoid a large pill burden, the participants are receiving matching placebo film-coated tablets for each corresponding tablet strength. Hence, the patients, the investigators and study personnel are double blinded in terms of who receives active or placebo, but given the different film-coated tablet sizes and number of tablets to digest, one can discern if either [redacted]/placebo or [redacted]/placebo is given and, thus, the study is labelled as single-blind. The study is designed to demonstrate efficacy versus placebo; a placebo control arm in the trial will enable placebo-corrected analysis of safety and efficacy.

Treatment period is extended up to 12 weeks to assess the sustained effects of AZD5718 on the prolonged inhibition of 5-LO pathway mediated inflammation, following the impact of initial 4-week treatment duration.

Based on information available, 4 weeks treatment duration is capable to decrease the level of leukotriene-mediated inflammation, though, prolonged treatment (up to 12 weeks) with 5-LO inhibitor showed significant reduction in blood (LTB_4) and urine (LTE_4) leukotriene levels and suggested potential influence on atherosclerosis (Tardif JC et al 2010).

In the current study, with CAD population of post-ACS patients, with the LAD stenosis less than 50% and TIMI flow ≥ 2, macrovascular component of coronary function and echo parameters probably will demonstrate rapid improvement on top of standard care initiated during the ACS. However, cardiac microvascular function seems to be dynamic in nature and noticeable improvements in CFVR with pharmacotherapy have been induced within 8 weeks treatment (Tagliamonte E et al 2015).

Consequently, treatment prolonged up to 12 weeks will allow to achieve and to assess sustained inhibition of leukotriene-mediated inflammation (urine-LTE_4 and blood-LTB_4) following the initial decrease after 4 weeks treatment. In addition, treatment with AZD5718 prolonged up to 12 weeks will allow to assess sustained dynamics, gradual and steady improvement of myocardial microvascular function (coronary flow reserve and echocardiography parameters) in post-ACS patients on top of long-term Standard of Care.

Extended up to 12 weeks treatment period will provide with more complete AZD5718 safety and tolerability profile with longer treatment exposure, on top of long-term Standard of Care in post ACS patients with CAD and support further clinical development.

The result of the study with prolonged treatment will facilitate the scientific and clinical basis for further investigation of AZD5718 in improving cardiovascular mortality and morbidity in CAD population.

CAD patients within four weeks after an ACS, either ST-segment Elevation Myocardial Infarction (STEMI) or non-ST-Segment Elevation Myocardial Infarction (NSTEMI), are chosen in order to have a population similar to the future target population. The patients will be recruited immediately after an ACS and treatment will commence earliest on day 7 after an

ACS. Since reproduction toxicology studies have not yet been conducted with AZD5718, females of child-bearing potential are excluded from the study and males are required to abstain from fathering a child or donating sperm for the same reason.

Collection of blood samples for potential future exploratory research into biomarkers related to coronary artery disease or that may influence drug response to AZD5718, has been included in the study. In addition, blood samples for potential current and future exploratory genetic research will be collected in patients who have given a separate consent for genetic research.

1.2.1 Dosing rationale

Single doses of up to [redacted] AZD5718 and once daily repeated doses of [redacted] and [redacted] for 10 days have been well tolerated in healthy subjects. The doses of [redacted] to be evaluated in this study are substantially lower than the highest single doses of AZD5718 studied. The [redacted] dose is considered to be a relevant therapeutic dose/exposure at steady state where more than 90% target inhibition over 24 hours is aimed for defined as *ex vivo* LTB_4 production in whole blood following stimulation with calcium ionophore. Model predicted relationship between inhibition of *ex vivo* LTB_4 production in blood and exposure in the Single and Multiple Ascending Dose (SMAD) study has shown that a [redacted] once daily dose at steady state gives 90% inhibition in approximately 90% of the subjects. The [redacted] dose is expected to give around 90% inhibition of u-LTE_4 over 24 hours and by its inclusion a wider dose/exposure range is being evaluated.

1.3 Benefit/risk and ethical assessment

AZD5718 has been administered to 84 healthy subjects (in completed studies or studies in reporting phase) in single doses up to 1200mg, and in repeated doses up to 600 mg for 10 days. The compound has been well tolerated in healthy subjects. No clinically meaningful differences for changes over time in clinical laboratory tests, vital signs or electrocardiograms (ECGs) were observed between subjects who received AZD5718 and those who received placebo. There were no deaths or serious adverse events (SAEs) and all subjects completed the studies. The most common adverse event (AE) was headache. No safety concerns were raised during the studies.

Preclinical safety studies have identified several potential risks including transaminase elevations, pharyngeal and gastric mucosal lesions and delayed gastric emptying, plasma glucose elevation, minimal hypertrophy of thyroid follicular cells and potential effects on heart rate and blood pressure. None of these findings were observed in the clinical studies performed to date. The preclinical safety findings are described in more 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 to this trial. Available preclinical and clinical data suggest that the subjects may benefit from participation in the study as inhibition of 5-LO pathway may improve coronary microvascular function, reduce coronary artery plaque progression and

improve left ventricle ejection fraction. Based on prior SMAD study, the effect of AZD5718 can be detected in decreased u-LTE_4 concentrations under the designed 4weeks of study treatment period, though potentially reaching even more stable and sustainable effect with the treatment prolongation up to 12 weeks.

The extended treatment period up to 12 weeks, will also provide with more complete safety profile data in CAD patients (post-ACS population) with longer treatment exposure.

The essential imaging modality in the trial is cardiac ultrasound. The Transthoracic colour Doppler Echocardiography (TDE) with CFVR measurement has the advantage of being non-radioactive, non-invasive and utilizing equipment readily available in the departments of cardiology. The cardiac ultrasound examination itself does not involve any discomfort. To measure the ability to increase blood flow, intravenous adenosine will be used in connection to the ultrasound examination. Adenosine is approved as tool for cardiovascular examinations. It can provide a fast and transient (one minute) heat sensation and a slight chest discomfort. The most common adverse reactions are warmth, shortness of breath, flushing and headache. In rare cases, heart palpitations, nausea, anxiety or blurred vision may occur. Under the medical attention provided in this trial, ultrasound CFVR measurement with adenosine infusion is not considered to pose a risk for the patients.

1.4 Study Design

This is a randomized, single-blind, placebo-controlled, parallel-group, multicentre study in subjects with CAD.

NB. The study was originally designed to be a 4-week study and was amended to be a 12-week study. As a consequence, some patients will have a treatment period of 4 weeks only while others will have a treatment period of 12 weeks. Visits 4b and 4c only apply to patients included under the amended CSP.

The study will be conducted at approximately 10 centres in 3 countries (Denmark, Finland and Sweden).

Patients suitable for the study will be identified and screened for eligibility after being hospitalized for ACS (Visit 1) comprising STEMI or NSTEMI. At Visit 1, after signing informed consent, biomarker sampling will take place at days 1, 2, 3 and 5 post ACS, where feasible. It is planned that approximately 138 CAD patients will be randomized to ensure at least 66 evaluable patients receiving AZD5718 [redacted] or placebo are included with 12 weeks treatment. An evaluable patient is defined as a patient with a valid CFVR measurement at Visit 2 (baseline) and one postbaseline visit as judged by the CFVR Core lab. For supporting dose selection in future studies, a treatment arm with 20% of randomized patients receiving AZD5718 [redacted] is included in the study.

On Day 1 (Visit 2), 7-28 days after the ACS event, patients willing to participate in the study will complete the screening procedure and, if eligible, be randomized in a ratio 2:1:2 to receive either AZD5718 ( ), AZD5718) or Placebo. Treatment duration will be 12 weeks, once daily administration in the morning. Dose on Visit 2 (Day 1), Visit 3 (2 weeks), Visit 4 (4 weeks), and Visit 4c (12 weeks) will be given by study personnel at the study site.

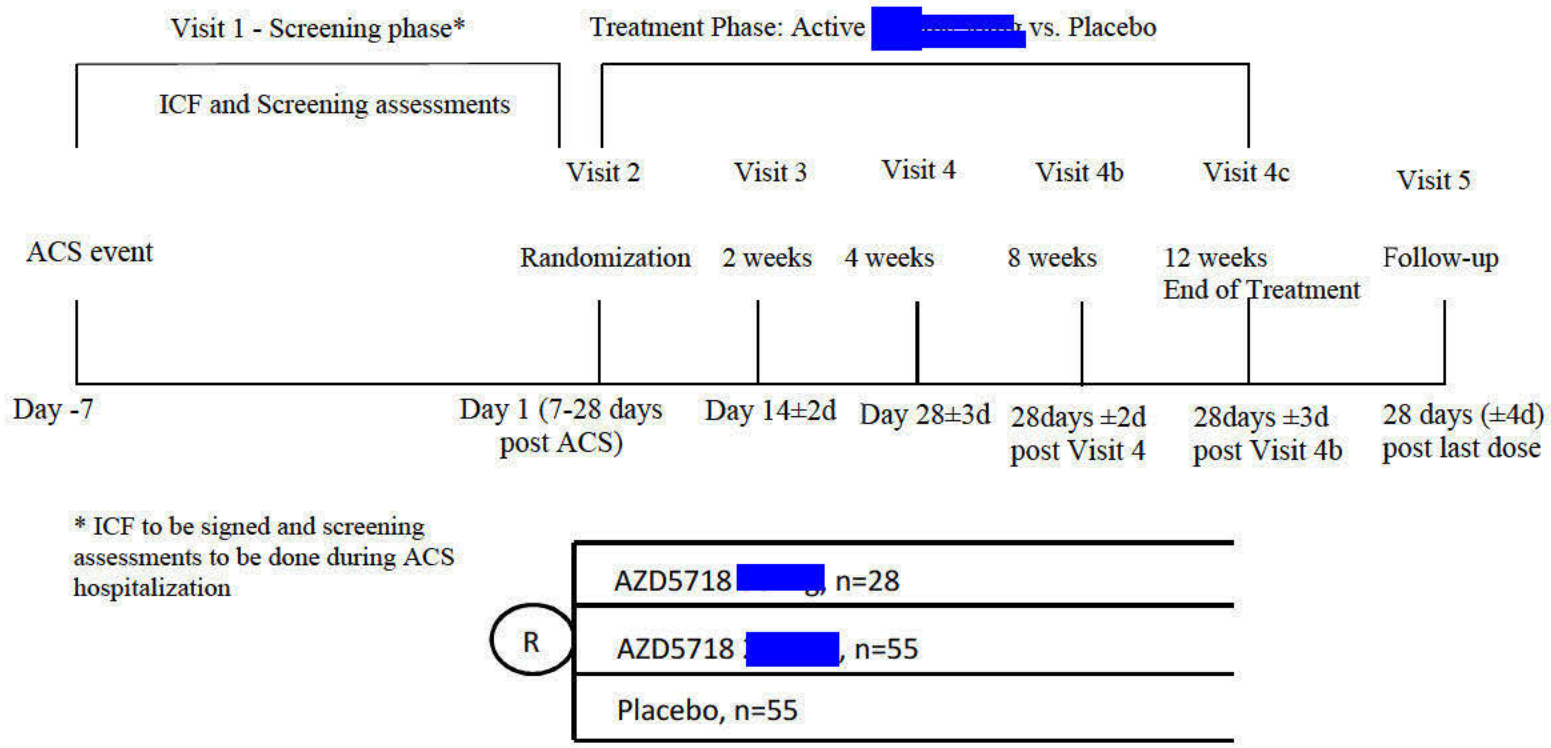
During the treatment phase, patients will come in to the clinic for study measurements at 2 weeks (Visit 3), 4 weeks (Visit 4), 8 weeks (Visit 4b) and 12 weeks (Visit 4c).

A follow-up visit (Visit 5) will be performed at 4 weeks (±4 days) after last dose in order to ensure safety and well-being of the patients.

Study overview is presented in Figure 1 below. For details and timings of the study assessments refer to Table 1 Section 4.

Based on emerging data from the study AstraZeneca may decide to use the plasma/serum and/or urine samples collected in the study to address other study objectives than the pre-specified for a specific sample.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the pharmacodynamics (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 4 weeks in CAD patients.	Percentage change from baseline in levels of u-LTE_4 (see Section 8.4.1)

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
• To assess the pharmacodynamics (PD) effect of AZD5718 by assessment of urine-leukotriene E4 (u-LTE_4) at 12 weeks in CAD patients.	Percentage change from baseline in levels of u-LTE_4 (see Section 8.4.1)
• To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 12 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)
• To assess the effect of AZD5718 on change from baseline in Coronary Flow Velocity Reserve (CFVR) at 4 weeks in CAD patients.	Change from baseline in Coronary Flow Velocity Reserve (CFVR) in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE)
• To assess the pharmacokinetics (PK) of AZD5718 after repeated oral dosing at 4 and 12 weeks in CAD patients	Standard model population pharmacokinetic (PK) parameters to be reported in a separate report
• To assess the effect of AZD5718 on coronary flow parameters at 4 weeks in CAD patients	Change from baseline in: – LAD resting mean diastolic flow velocity – LAD hyperaemic flow velocity
• To assess the effect of AZD5718 on change in echocardiographic parameters at 4 weeks in CAD patients.	Change from baseline in: – Left Ventricular (LV) Ejection Fraction (LVEF) – LV global longitudinal strain (GLS) – LV global circumferential strain (GCS) – LV longitudinal early diastolic strain rate

2.3 Safety objectives

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

2.4 Exploratory objectives

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

variations that may affect PK, PD, efficacy, safety and tolerability related to AZD5718 treatment

Note: For details regarding exploratory variables, measurements and analyses refer to Sections 8.4.3, 8.5.5 and 5.3.1 (Table 4).

3. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, 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.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Males and females:
   a. Males must be surgically sterile or using an acceptable method of contraception (see Section 3.8.4)
   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
2. Age ≥18 to ≤75
3. BMI ≥18 to ≤35 kg/m^2
4. CAD patients, here defined as:
   a. ACS 7-28 days prior to study randomization (ACS defined as STEMI, non-STEMI event documented by ECG, cardiac enzymes [troponin] and angiogram)
   b. Possible post procedure LAD stenosis is <50% and TIMI flow is ≥ 2
5. Provision of signed and dated, written informed consent prior to any study specific procedures

3.2 Exclusion criteria

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

1 Alanine aminotransferase (ALT) >2 x ULN (i.e., above the normal range) at visit 2, cirrhosis, recent hepatitis, or positive screening test for hepatitis B (hepatitis B surface antigen) or hepatitis C

2 Uncontrolled Type 1 or Type 2 diabetes defined as haemoglobin A1c (HbA1c) Diabetes Control and Complications Trial (DCCT)> 9% or International Federation of Clinical Chemistry (IFCC) >74.9 mmol/mol

3 Patients with atrial fibrillation (chronic or current) or history of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia or sick sinus syndrome or AV blockage degree 2-3

4 Patients with pacemaker

5 Prior coronary artery by-pass graft (CABG) to LAD

6 Left ventricle ejection fraction < 30%

7 Unacceptable level of angina despite maximal medical therapy or unstable angina at entry Canadian Cardiovascular Society (CCS) ≥ 3 (Visit 1 or Visit 2)

8 Stroke within the previous 6 months from ACS or ongoing treatment with Persantin or Asasantin

9 Planned treatment with zileuton, leukotriene receptor antagonists (e.g. montelukast), coumadin or steroids during trial

10 Planned statin therapy dose regimen changes during trial

11 Chronic use of anticoagulants on therapeutic dose (not including thrombosis prophylaxis) during the study

12 Planned additional cardiac intervention (e.g., PCI, CABG) within next 6 months

13 NYHA class III-IV heart failure or decompensated heart failure at discharge or hospitalization for exacerbation of chronic heart failure within the previous 3 months from ACS

14 Previously known severe renal disease (CKD stage 4 or 5) or previously known creatinine clearance calculated by Cockcroft Gault equation <30 ml/min*m^2

15 Aortic or mitral valvular disease or valvular disease classified as severe

16 Known allergy to adenosine and mannitol, or experience of previous adverse effects of adenosine stress testing

17 Known elevated intracranial pressure

18 Heart rate < 40 bpm

19 Systolic blood pressure < 90 mmHg

20 Asthma or COPD with strong reactive component in judgment of investigator

21 Treatment with dipyridamole, theophyllamine, fluvoxamine, rifampicin, fenytoin or carbamazepine

22 Inability to comply with the study protocol

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

24 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

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

26 Participation in another interventional clinical study with an investigational pharmaceutical product during the last 3 months also including drug eluting stents

27 Previous randomization in the present study

28 Known history or current abuse of drugs or alcohol

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

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

2. Assign (using the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS)) potential study patient a unique enrolment number, beginning with 'E#

3. Determine patient eligibility. See Section 3.1 and 3.2

4. Assign enrolled patient a unique randomization code (patient number) in IVRS/IWRS at Visit 2. See Section 3.5

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

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.

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 the patient must discontinue the treatment and be**

withdrawn from the study. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

At randomization the IVRS/IWRS will assign eligible patients a unique randomization code and blinded investigational product (IP) kit number(s) to the patient. Specific information concerning the use of the IVRS/IWRS will be provided in the separate user manual.

Block randomization using IVRS/IWRS will be used to randomize patients in a 6:3:4:2 ratio to receive a fixed dose of AZD5718 [redacted], AZD5718 [redacted], placebo [redacted] or placebo [redacted]. Upon completion of the randomization request form, the randomization will be produced by PAREXEL Informatics using the AstraZeneca randomization solution (AZRand).

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

3.6 Methods for ensuring blinding

The study will have a single blind design. Placebo film-coated tablets will match appearance of each AZD5718 film-coated tablet strength. Identical package configuration will be used for each placebo tablets and AZD5718 tablet strength.

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

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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 IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

For the interim analysis, independent personnel with no other involvement in the study will be unblinded to certain data. A detailed description of the interim analysis including the unblinding process will be included in the interim analysis plan.

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 subject with restriction violation will be allowed to continue study participation

3.8.1 Medication 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

- Patient should arrive at the clinic after fasting overnight (no food or liquid [except for water] intake permitted from 10 p.m. the evening before) for Visits 2, 3, 4, 4c and 5 for sampling for PK/PD and safety assessments. CFVR measurement at Visits 2, 4 and 4c requires fasting for at least 4 hours
- Abstain from use of grapefruit juice and St John's Wort during the study

3.8.3 Alcohol, Drugs of abuse, Tobacco and Caffeine Restrictions

- Prior to Visits 2, 4 and 4c, avoid intake of coffee or other caffeine containing beverages 12 hours before and until after completion of the study specific clinical assessments (CFVR, Echo)
- Abstain from tobacco/nicotine for at least 120 minutes prior to CFVR measurements, or whenever study procedures demand it. Nicotine substitutes will be offered at the discretion of the Investigator
- Abstain from alcohol for 48 hours preceding the clinical visits
- Abstain from drugs of abuse during the entire study

3.8.4 Restrictions for male study subjects

Male subjects 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 the last dose of IP (AZD5718/matching placebo) to prevent pregnancy in partners.

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

3.8.5 Other Restrictions

Subjects who are blood donors should not donate blood during the study and for 3 months following their last dose of AZD5718.

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
- An adverse event that, in the opinion of the Investigator or AstraZeneca, warrants discontinuation from further dosing
- Patient noncompliance that, in the opinion of the Investigator or sponsor, warrants withdrawal (e.g. refusal to adhere to scheduled visits)
- Patient is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing IP, in the decision of the Investigator, might constitute a safety risk

If the patient is discontinued from IP, the scheduled study visits, data collection and procedures should continue according to the Clinical Study Protocol (CSP) until study closure. Alternatively, if the subject 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 subject and in compliance with local data privacy laws/practices. The approach taken should be registered in the CRF.

If patient is required to or chooses to discontinue the IP, every reasonable effort should be made for the patient to remain in the study for follow-up and to complete all other study procedures until the scheduled end of the study.

3.9.1 Procedures for discontinuation of a subject from IP

At any time, patients are free to discontinue IP or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); diary cards, and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients 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 (IP 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.

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

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 IP,
- 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, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

4.1 Study Procedures

General information

For Visits 2, 3, 4, 4c and 5, patients will come to the clinic in the morning after fasting overnight (see 3.8.2).

Patients will record drug intake in diary cards for out-patient administration of IP. Diary cards will be handed-out to the patients after randomization at Visit 2 and reviewed during subsequent visits and at the end of treatment (Visits 3, 4, 4b and 4c).

For the full list of assessments and sampling/measurement time points, see assessment schedule (Table 1).

Visit 1 (Screening)

Visit 1 will take place at the clinic during the in-house hospital stay post ACS-event. It should be noted that Visit 1 can last over several days. Biomarker sampling, where feasible, will take place at 1, 2, 3 and 5 days post ACS. If the patient is discharged from hospital early, he/she may be asked to come back for biomarker sampling.

- Screening of patients will be done by review of hospital medical records and by evaluation of inclusion and exclusion criteria. 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 Informed Consent Form (ICF). Medical and Surgical History will be collected.
- ACS-related in-hospital invasive coronary angiogram is required to assess Thrombolysis-In-Myocardial-Infarction (TIMI) flow score from the three epicardial coronary arteries.
- Patients will be assessed for GRACE Score (Global Registry of Acute Coronary Events GRACE) - a ACS Risk Calculator that provides the percentage probability of death or death/MI at time-points up to 3 years following admission with ACS.
- Measurements and sampling for PD (u-LTE_4), safety and exploratory variables will be performed.

Visit 2 (Randomization)

- Patients will arrive at the clinic after fasting overnight and baseline sampling (PD [u-LTE_4], exploratory biomarkers and safety lab [incl. liver panels]), clinical assessments (physical examination, vital signs, and ECG) and AE-review will be conducted.
- Screening will be completed by evaluation of inclusion and exclusion criteria

- Patients will undergo baseline measurements for secondary and exploratory endpoints (cfPWV/bPWA, CFVR and echocardiography).
- Randomization and dosing will take place after baseline assessments in the morning.
- After randomization the following assessments will be conducted: PRO assessments and sampling for PK
- In case of sustained discomfort after CFVR measurement, the patient should stay at the clinic until 2 hours after status stabilization.
- IP for the first 4 weeks will be dispensed

Visit 3 (2 weeks, During Treatment)

- Visit including AE-review, clinical safety assessments, collection of samples and IP intake at the clinic

Visit 4 (4 weeks, During Treatment)

- The following assessments will be conducted during the visit: urine collection for assessment of LTE_4, sampling for PK, safety and exploratory biomarkers as well as measurement of clinical safety, efficacy and exploratory endpoints such as BP, ECG, CFVR, cfPWV/bPWA, echocardiography and PRO questionnaires
- The dose will be taken at the clinic and the patients will return the remaining IP and receive a new bottle of IP for weeks 5-8
- The patients will leave the clinic after completed measurements, but in case of sustained discomfort after CFVR measurement, the patient should stay until 2 hours after status stabilization.

Visit 4b (8 weeks, During Treatment)

- Visit including AE-review, concomitant medication review
- The patient will return the remaining IP and receive a new bottle of IP for weeks 9-12

Visit 4c (12 weeks, End of Treatment)

- The following assessments will be conducted during the visit: urine collection for assessment of LTE_4, sampling for PK, safety and exploratory biomarkers as well as measurement of clinical safety, efficacy and exploratory endpoints such as BP, ECG, CFVR, cfPWV/bPWA, echocardiography and PRO questionnaires
- The last dose will be taken at the clinic and the patient will return the remaining IP

- The patient will leave the clinic after completed measurements, but in case of sustained discomfort after CFVR measurement, the patient should stay until 2 hours after status stabilization.

Visit 5 (Follow-up)

- In the morning, urine collection for assessment of LTE_4, clinical assessments and sampling for PK, safety and exploratory biomarkers as well as measurement of clinical safety, efficacy and exploratory endpoints such as BP, ECG, cfPWV/bPWA and echocardiography.

Table 1 Study assessment schedule

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

Table 1 Study assessment schedule

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

Table 1 Study assessment schedule

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

Table 1 Study assessment schedule

	ACS event	Visit 1 Screening	Visit 2 Randomization	Visit 3 (2 weeks) During Treatment	Visit 4 (4 weeks) During Treatment	Visit 4b (8 weeks) During Treatment	Visit 4c (12 weeks) End of Treatment	Visit 5 Follow-up	Comments
Study Day	**-7 days**	**x[a]**	**day 1**	**day 14**	**day 28**	**28 days after Visit 4**	**28 days after Visit 4b**	**28 days after last dose**	
Time Window		**1-5 days post ACS event**	**7-28days post ACS event**	**±2**	**±3**	**±2**	**±3**	**±4 days**	
CFVR measurement			x		x		x		
Echocardiography			x		x		x	x	
cfPWV/bPWA			x		x		x	x	
Pharmacokinetics:									
Plasma for AZD5718			x[h]	x[i]	x[j]		x[i]	x[k]	
Exploratory Clinical Variables:									
-PRO questionnaires			x (post-dose)		x (post-dose)		x (post-dose)		
-GRACE 2.0 Score		x							
Exploratory Biomarkers:									
-Plasma for analysis of LTB_4 levels		x[l]	x (pre-dose)	x (pre-dose)	x (pre-dose)		x (pre-dose)	x	

Table 1 Study assessment schedule

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

a Screening during in-house stay after ACS event. Assessments can take place over several days. If the patient is discharged from hospital early, he/she may be asked to come back for blood sampling.
b Body weight assessments to be conducted in the mornings after an overnight fast, except for non-fasting at screening (Visit 1)
c Full physical examination at Screening (Visit 1) and at Follow-up (Visit 5), and brief physical examination on the other occasions (Visits 2, 3, 4 and 4c).
d Fasting plasma samples for glucose measurements to be obtained after an overnight fast (from 10 p m. the evening before) at the same time point at Visits 2, 3, 4, 4c and 5 to the extent possible.
e Will exclude fasting glucose measurement.
f Liver panel analyses results will be used for assessment of exclusion criteria. Samples need to be analysed as acute samples.
g Spot urine sample to be collected in the morning prior to screening and baseline assessments.
h Baseline sample to be obtained in the morning before screening assessments. The other sample to be taken between 1-8 h post-dose.
i C_{Trough} sample to be collected before dose administration at 20-28 hours after previous dose (dose on day 13 (day before Visit 3) and on day before Visit 4c).
j Sampling times: pre-dose and then 0-2 h, 2-4 h, 4-8 h post dose. Sampling will be separated with at least 1 hour.
k One PK-sample to be collected as suitable in relation to the other follow-up measurements. Exact sampling time to be entered in the CRF.

l Sampling, where feasible, at 1, 2, 3 and 5 days post ACS. Exact sampling time to be entered in the CRF.
m Unscheduled safety assessments (blood and urine samples for safety lab and ECG) may be performed as judged by the investigator
n Will exclude TSH, Free T3, Free T4 and Total T4
o The genetic sample may be collected at any time after randomization, however, ideally samples should be collected at Visit 2

Order of assessments:

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

4.2 Screening/Enrolment period

Procedures will be performed according to the Study Plan in Table 1.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

4.3 Treatment period

Descriptions of the procedures for this period are included in Section 4.1 and in the Study assessment schedule (Table 1).

4.4 Follow-up period

Descriptions of the procedures for this period are included in Section 4.1 and in the Study assessment schedule (Table 1).

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 (eCRFs) as specified in the CSP 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 (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Urine-leukotriene E4 (u-LTE_4)

Efficacy will be evaluated by assessment of change from baseline of creatinine-normalised urine-leukotriene E4 (u-LTE_4) measured in spot urine.

For timings of the assessments refer to Section 4 and Table 1.

Details of the sampling and analyses will be given in the Laboratory Manual.

5.1.2 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-

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

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 Manual of Procedures (MoP) for Echocardiography (detailed echocardiography protocol) that will be supplied to all study sites. Doppler and tissue Doppler echocardiography will be performed to obtain indices necessary for comprehensive assessment of left ventricular (LV) diastolic function and non-invasive hemodynamic measurements, as detailed in MoP.

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

Coronary flow velocity reserve is measured in the LAD coronary artery before, and during constant adenosine infusion at a rate of 140 µg/kg/min for 1-5 minutes using conventional colour Doppler ultrasound equipped with coronary imaging protocol. For details see MoP.

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

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

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, serology and urinalysis will be taken at the times indicated in the Study Plan (see Section 4, Table 1).

The clinical chemistry, haematology, serology 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 following laboratory variables will be measured:

Table 2 Standard Clinical Laboratory Evaluation Panels

Haematology/Haemostasis (whole blood)	Clinical Chemistry* (serum or plasma)
White blood cell (WBC) count	Sodium
Red blood cell (RBC) count	Potassium
Haemoglobin (Hb)	Urea
Haematocrit (HCT)	Creatinine
Mean corpuscular volume (MCV)	Albumin

Haematology/Haemostasis (whole blood)	Clinical Chemistry* (serum or plasma)
Mean corpuscular haemoglobin (MCH)	Calcium
Mean corpuscular haemoglobin concentration (MCHC)	Phosphate
Neutrophils absolute count	Glucose (fasting) (Not at Visit 1 - Screening)
Lymphocytes absolute count	Alkaline phosphatase (ALP) "LIVER PANEL"
Monocytes absolute count	Alanine aminotransferase (ALT) "LIVER PANEL"
Eosinophils absolute count	Aspartate aminotransferase (AST) "LIVER PANEL"
Basophils absolute count	Total bilirubin "LIVER PANEL"
Platelets	FSH (Screening only)
Reticulocytes absolute count	LH (Screening only)
Coagulation	TSH, Free T3, Free T4, Total T4
International normalized ratio (INR)	
Activated partial thromboplastin time (APTT)	
Fibrinogen	
	Urinalysis
	Glucose (dipstick)
	Albumin (quantification/semi-quantification)
	Protein (dipstick)
	Blood (dipstick)
	WBC (Leukocytes) (dipstick)
	Creatinine (quantification)

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

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

Table 3 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

5.2.2 Physical examination

A complete physical examination will be performed at Screening (Visit 1) and at Follow-up (Visit 5) and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities) and neurological systems. On the other occasions (Visit 2, 3, 4 and 4c) a brief physical examination (general appearance, skin, abdomen and musculoskeletal, cardiovascular and respiratory systems) will be conducted.

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

5.2.3 Body weight

Body weight assessments will be conducted in the mornings after an overnight fast (except for non-fasting at screening) with the patients in underwear/light clothes and after a lavatory visit. Assessments are to be done on the same calibrated scale at all occasions.

5.2.4 ECG

12-lead ECG recordings will be collected according to the assessments schedule presented in Section 4, Table 1. The investigator will make an overall evaluation of the ECG as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

Abnormal values shall not be recorded as AEs unless deemed clinically significant. 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 later available to adjudicate in case of events.

Digital ECGs refers to the storage of digital safety ECG source files that are retrievable for adjudication if required. The study will be performed in an unstable ischemic cardiac population with increased cardiovascular risk and primarily the ECGs will be assessed in real time for safety signals by experienced ECG readers as part of the standard clinical safety evaluation on site.

Based on data from the phase I studies, no trends or findings of safety concerns on any ECG parameter have been identified.

5.2.4.1 Resting 12-lead ECG

The following parameters or time intervals will be recorded for each ECG: RR, PR, QRS, QT, QTcF and heart rate (HR).

5.2.5 Vital signs

Vital signs will include pulse, and systolic and diastolic blood pressure. Vital signs will be obtained at time points indicated in Section 4, Table 1(and ad-hoc as medically indicated).

5.2.5.1 Pulse 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.

5.3 Other assessments

5.3.1 Other research biomarker assessments

Samples for additional research biomarker assessments will be collected at time points listed in the schedule of assessments in Section 4. Table 1. The research biomarkers are listed in Table 4.

Table 4 Research biomarkers

Panel Name	Biomarkers
FLAP Biomarkers	Plasma LTB_4
Cardiovascular Biomarkers	Proseek Multiplex CVD II $^{96\times96}$ panel
	Proseek Multiplex CVD III $^{96\times96}$ panel
	Lipid profile (total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides)*
	hsTnI (high sensitive Troponin I)

Panel Name	Biomarkers
	hsCRP (High-sensitivity C-Reactive Protein)
	NT-proBNP (N-Terminal Prohormone of Brain Natriuretic Peptide)
	Lp(a)* (Lipoprotein a)
	GDF 15 (Growth/differentiation factor 15)
	MPO mass (Myeloperoxidase protein level measurement)
	IL-6 (Interleukin 6)
	IL-1B (Interleukin 1 beta)
	ApoA1* (Apolipoprotein A)
	ApoB*

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

5.3.2 Clinical Outcome Assessments

PRO questionnaires will be used to address exploratory objectives.

Two general health-related quality of life instruments will be applied: SF-36 and EQ-5D.

Both dyspnoea and fatigue symptoms are of particular relevance in patients with CAD and ACS. For assessment of dyspnoea Rose Dyspnoea Score will be administered and FACIT fatigue scale will be used to assess fatigue.

The PRO questionnaires used in this study will all be collected by paper, subject-self completed and do not require training. Site personnel 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 15 min. The questionnaires to be used are listed below:

- SF-36 V2 (The Short Form (36) Health Survey - a 36-item, patient-reported survey of patient health. SF-36 is a general well-validated questionnaire which encompasses eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.)
- EQ-5D-5L™ from EuroQol Group (a 5-dimensional, standardised instrument for use as a measure of health outcome applicable to a wide range of health conditions and treatments.)

- Rose Dyspnoea score (a standardized 4-item survey to measure patient related outcomes entailing symptoms of dyspnoea for patients with coronary artery disease.)

- FACIT-Fatigue scale (part of the FACIT Measurement System. Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale - a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities.)

The time points for the above listed PRO assessments are given in the schedule of assessments in Section 4, Table 1.

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

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

The subject 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.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Venous blood samples for the determination of plasma concentrations of AZD5718 will be collected at the time points presented in the study assessments schedule, Section 4, Table 1.

Placebo samples will only be analysed on Day 14, unless specified.

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

Standard model population PK parameters will be reported in a separate report.

5.4.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

5.4.3 Storage and destruction of pharmacokinetic samples

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

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

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.5 Pharmacodynamics

5.5.1 Collection of samples

Samples for determination of LTE_4 and creatinine in spot urine will be taken at the times presented in the study assessments schedule, Section 4, Table 1.

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

5.5.2 Storage, re-use and destruction of pharmacodynamics 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 any investigation will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

For storage and handling details of PD-samples refer to the Laboratory Manual.

5.6 Genetics (optional)

An optional genetic blood sample will be obtained from the study patients who have signed the genetic ICF. The genetic sample may be collected at any time after randomization, however, ideally samples should be collected at Visit 2 i.e. early in the study (see Table 1) to avoid bias in the sample collection (i.e. failure to collect samples from subjects who have suffered an AE etc.). Information regarding genetic research is detailed in Appendix C.

For details of sampling, handling, storage and transportation of the samples refer to the Laboratory Manual.

5.7 Biomarkers

The patient's consent to the use of donated exploratory research biomarker samples is mandatory.

Biological samples (e.g. blood samples) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of AZD5718, clinical outcomes and toxicity.

Samples for determination of research biomarkers (see Section 5.3.1, Table 4) will be taken at the times presented in the study assessments schedule, Section 4, Table 1.

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

5.7.1 Storage, re-use and destruction of biological samples

Exploratory biomarker research 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 AZD5718 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 Study Protocol 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 Gothenburg 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.

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

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject 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 and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject 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 CSP.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of the first dose throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing ICF.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the 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 collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- 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
- 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 IP and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

A guide to the interpretation of the causality question is found in Appendix A to the CSP.

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 CSP mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs 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 IP.

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).

If clinically non-significant ECG findings are reported they are not required to be recorded as AEs, unless there are clinical symptoms and actions taken that merit for AE/SAE reporting on their own.

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 D 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 IP, 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 AZD5718 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 if the pregnancy is discovered before the study subject 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, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the 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.

Sperm donation

Male subjects 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 recognized 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 (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

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

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 5 Investigational products – dosage form and strength

Investigational product	Dosage form and strength	Dose	Manufacturer
AZD5718	[redacted] of AZD5718 [redacted] tablet	[redacted]	AstraZeneca
AZD5718	[redacted] of AZD5718 [redacted] tablet	[redacted]	AstraZeneca
Placebo to match (PTM) AZD5718 [redacted]	PTM AZD5718 [redacted] tablet	[redacted]	AstraZeneca
Placebo to match (PTM) AZD5718 [redacted]	PTM AZD5718 [redacted] tablet	[redacted]	AstraZeneca

AstraZeneca R&D Supply Chain (or contract research organisation) will pack, label, and supply AZD5718 and matching placebo for this study.

AZD5718 and Placebo will be packed into white high-density polythene bottles with child resistant, tamper evident closures. Study drug must be kept out of the reach of children.

7.2 Dose and treatment regimens

On Day 1 (Visit 2), 7-28 days after the ACS event, patients willing to participate in the study will complete the screening procedure and if eligible be randomized to a once daily administration, to be taken with approximately 200 ml water in the morning with no restrictions on food intake. Randomized patients will be dispensed with one bottle of IP at each dispensing visit. Dispensation will take place at the following study visits: Visit 2 (Randomization), Visit 4 (4 weeks), Visit 4b (8 weeks), see Table 1. Dose at Visit 2 (day 1), Visit 3 (day 14), Visit 4 (4 weeks) and Visit 4c (week 12) will be given by study personnel at the study site following an overnight fast. The exact dose intake time before Visit 3, Visit 4 and Visit 4c will be recorded on a Diary Card. The Diary Cards will be given to the patients at the randomization visit and the patients will be asked to fill in the dose intake information (date and time) at home.

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 IP label on the bottle specifies the appropriate storage.

7.5 Compliance

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

7.6 Accountability

The IP provided for this study will be used only as directed in the CSP.

The study site staff will account for all IPs dispensed to and returned from the patient.

IP kits will be uniquely coded and assigned through the randomization and subsequent visits via the IVRS/IWRS. On receipt of IP supplies the Investigator/designee will check the supplies against the shipment manifest and will confirm receipt of IP shipments via the IVRS/IWRS. The system will then issue an acknowledgement receipt. Sites are required to place all shipment manifests and acknowledgement receipts in the site regulatory binder.

The study site staff is also responsible for maintaining accurate records accounting for the receipt, dispensing and final disposition of all IPs using the appropriate IP logs provided by AstraZeneca.

7.7 Concomitant and other treatments

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

Prohibited Medication/Class of drug:	**Usage:**
Zileuton, leukotriene receptor antagonists (e.g. Montelukast), Coumadin or steroids during study Rifampicin, Fenytoin, Carbamazepine	Planned or ongoing treatment during the study
Persantin or Asasantin. Dipyridamole, Theophyllamine or Fluvoxamine	Ongoing treatment at entry and during the study
Anticoagulants on therapeutic dose (not including thrombosis prophylaxis)	Chronic use, during the study

7.7.1 Other concomitant treatment

Other medication 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

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol violations. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to the interim analysis. 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 analyses will be fully documented in the SAP.

8.2 Sample size estimate

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

The Hierarchical testing sequence for the four endpoints are:

1. u-LTE_4 at 4 weeks
2. u-LTE_4 at 12 weeks
3. CFVR at 12 weeks
4. CFVR at 4 weeks

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

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

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

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

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

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

8.3.2 Safety analysis set

The safety analysis set will include all patients who were randomized and received at least one dose of study medication. Patients will be analysed according to the treatment which they actually received. If a patient received IP from the wrong kit for only a part of the treatment duration and then switched to another, the associated treatment group for that patient will be the treatment group that patient was randomized to. Any important protocol deviations from randomized treatment will be listed and considered when interpreting the safety data. Important protocol deviations will be defined in the SAP.

8.3.3 PK analysis set

The PK analysis set will consist of all patients in the efficacy analysis set who has received at least one dose of AZD5718, and who has at least one PK sample post dose.

8.4 Outcome measures for analyses

8.4.1 Efficacy variables

The primary efficacy variable is percentage change at Visit 4 from baseline (Visit 2) in creatinine-normalised u-LTE_4. Summary statistics per time point the variables are measured will also be presented.

The following secondary efficacy variables are all measured as change from baseline (Visit 2):

- u-LTE_4 at week 12
- CFVR at week 4 and 12

- LAD resting mean diastolic flow velocity
- LAD hyperaemic flow velocity
- Measurements of left ventricular (LV) systolic and diastolic function, more specifically
  - LV ejection fraction (LVEF) at rest
  - LV Global Longitudinal Strain (GLS) at rest and at hyperaemia
  - LV Global Circumferential Strain (GCS) at rest
  - LV longitudinal early diastolic strain rate

Summary statistics per time point the variables are measured will also be presented.

8.4.2 Safety variables

Adverse Events, vital signs (blood pressure and pulse rate), physical examination, clinical laboratory safety evaluations (haematology, serum biochemistry and urinalysis [see Table 2 and Table 3]) and 12-lead ECG.

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

8.4.3 Exploratory variables

- Carotid-femoral pulse wave velocity and brachial pulse wave analysis (cfPWV/bPWA) parameters. The output variables – measured as change from baseline - will be:
  - Augmentation index,
  - Carotid-femoral pulse wave velocity
  - Pulse pressure amplification (derived variable)
  - Central pulse pressure
  - Central blood pressure systolic/diastolic
  - Brachial blood pressure systolic/diastolic

  Summary statistics per time point the variables are measured will also be presented.
- Quality of life questionnaires – measured as change from baseline:
  - SF-36 – overall score and per each dimension
  - EQ-5D – overall score
  - Rose Dyspnoea score – overall score
  - FACIT-Fatigue – overall score

Summary statistics per time point the variables are measured will also be presented.

- GRACE 2.0 Score at baseline

Exploration of changes in additional echocardiographic variables parameters that will be captured are to be referred in an exploratory SAP and results will be described in a separate report.

Variables handling exploration of the relationship between AZD5718 exposure and the exploratory objectives, as well as exploration of changes in efficacy and safety endpoints based on baseline assessments are also to be referred in an exploratory SAP and results will be described in a separate report.

8.4.4 Exploratory biomarkers

The exploratory research biomarkers are listed below and in Table 4.

- Cardiovascular biomarkers – measured as change from baseline:
  - hsTnI
  - hsCRP
  - NT-proBNP
  - total cholesterol
  - LDL-cholesterol
  - HDL-Cholesterol
  - Triglycerides
  - ApoA1
  - ApoB
  - Lp(a)

  Summary statistics per time point the variables are measured will also be presented.

Proseek Multiplex CVD II and CVD III panels, MPO mass, plasma LTB_4, GDF15, IL-1B, IL-6 and responder analysis of PD biomarkers, as well as genetic variations that may affect PK, PD, efficacy, safety and tolerability related to AZD5718 treatment are to be referred in an exploratory SAP and results will be described in a separate report.

8.5 Methods for statistical analyses

All efficacy and safety variables will be summarised by treatment groups using descriptive statistics (n, mean, geometric mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum for continuous data and absolute and relative frequencies for categorical data). Data will be summarised for baseline, endpoint and by visit (if applicable). P-values will be unadjusted and tests will be two-sided except for the primary efficacy variable, first secondary, second secondary and third secondary efficacy variable, which will have one-sided tests. All tests will be performed between the AZD5718 [redacted] group versus placebo, or the AZD5718 [redacted] group versus placebo.

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

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

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

To preserve the overall type1-error at 5% when testing the primary endpoint, first secondary, second secondary and third secondary endpoint a Hierarchical test procedure will be used as described in the section 8.2 Sample size estimate.

The statistical methods will be further detailed in the SAP.

8.5.1 Analysis of the primary variable(s)

The primary efficacy variable will test the null hypothesis that patients given AZD5718 [redacted] have less than 80% inhibition of u-LTE_4 compared to placebo, versus the alternative hypothesis that patients given AZD5718 have equal or more than 80% inhibition of u-LTE_4 compared to placebo (one-sided confidence interval) at week 4.

The primary efficacy variable will be analysed as change from baseline using a repeated measures model with type of MI (STEMI vs NSTEMI), time from randomization (days), treatment and time treatment interaction as fixed effects with baseline value as covariate. The covariance structure will be spatial power law covariance structures (generalisation of an auto regressive covariance structure allowing for none equidistant time points). All available data from each patient will be used for the analysis. The analysis will be done on loge scale. However, the result will be back transformed to original scale.

8.5.2 Analysis of the secondary variables

The first secondary, second secondary and third secondary efficacy variable will be analysed in the same type of model as for the primary endpoint, that is, a repeated measurement model with the same structure as described for the primary variable. All three endpoints will be measured as change from baseline and the analyses will be done on logarithmic transformed data. However, the result will be back transformed to original scale.

The models for analysis of all other secondary variables will be defined in the SAP. In general, an analysis of covariance or as a repeated measurement model will be used. The SAP will also describe which variable that will be analysed on original scale or on log scale. All results from transformed variables will be back transformed to the original scale.

If data permits a population PK model will be developed, possibly with the support of PK data from studies D7550C00001 and D7550C00002, using nonlinear mixed effects regression

analysis in NONMEM. Furthermore, if data allows, the population PK model may be coupled with separate PD models for u-LTE_4 and for CFVR.

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

8.5.3 Analysis of safety variables

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

- Baseline period: The time before first administration of IP.
- On treatment: The time from first administration of IP until 7 days after last dose of IP.
- Off treatment: More than 7 days after last dose of IP.

AEs will be assigned to the period where they start.

Laboratory data for haematology and clinical chemistry will be summarized by treatment group. The frequency of changes with respect to normal ranges between baseline and end of treatment will be tabulated. Shifts from normal to abnormal between baseline and end of treatment time point will be evaluated for urinalysis. Descriptive statistics might need to be applied to evaluate some of the reported urine laboratory values changes. 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.

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

8.5.4 Subgroup analysis

Type of MI (STEMI or NSTEMI) is used as a stratification factor in the randomization. For variables measuring change from baseline that uses type of MI as covariate in the model, estimates of change from baseline will be presented for each type of MI.

8.5.5 Exploratory analysis

All exploratory variables and biomarkers will be analysed in a similar way as the secondary variables. The models for analysis will be defined in the SAP. In general, an analysis of covariance or as a repeated measurement model will be used. The SAP will also describe

which variable that will be analysed on original scale or on log scale. All results from transformed variables will be back transformed to the original scale.

As described in section 8.4, there are exploratory variables and exploratory biomarkers where the analysis will be described in an exploratory SAP and results will be described in a separate report.

8.5.6 Interim analysis

Two administrative interim analyses will be conducted. The first one is planned after at least 45 patients have performed their CFVR measurement at Visit 4 and the second after at least 100 patients have performed their CFVR measurement at Visit 4. The variables for the analyses will be CFVR and LV Global Longitudinal Strain (GLS). These analyses will not have any impact on the overall type-1 error because no changes will be made to the trial based on the outcome of the analyses. The purpose with the interim analyses is to trigger external activities not connected to the trial. Both interim analyses will be performed by study independent personnel.

The models for the interim analysis will be analysed using Analysis of Covariance with treatment, type of MI (STEMI vs NSTEMI) and baseline value as covariates, with compound symmetry as covariance structure. Change from baseline will be used as endpoint and the analysis will be done on loge scale. The result will be back transformed to original scale.

For the second interim analysis, all data available will be used to measure change from baseline in a repeated measures model with treatment, type of MI, time (from randomization) and treatment*time interaction as fixed effects, baseline value will be used as covariate. The exact model will be prespecified in the interim analysis plan. Change from baseline will be used as endpoint and the analysis will be done on loge scale. The result will be back transformed to original scale

In the event of positive outcome at any of the administrative interim analyses an evaluation of exposure-response relationship may be performed. This analysis has the intention to guide the dose setting for the next study. This will be performed by non-study personnel with no other involvement in the study. Data for this analysis will be based on PK, u-LTE_4 and CFVR.

In connection to the first administrative interim analysis, a safety review committee (SRC) will be unblinded to safety data including AEs, SAEs and safety labs to ensure no safety concerns are associated with AZD5718 treatment.

An interim analysis plan will be prepared and finalized prior to the first administrative interim analysis. A separate analysis plan will also be prepared for the evaluation of exposure-response relationship and it should be finalised prior to the first administrative interim analysis

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca representative or delegate will review and discuss the requirements of the CSP 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 CSP, 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 subject'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 CSA 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 CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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 CSA 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 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 AZD5718.

9.4 Data management

Data Management will be performed by AstraZeneca/Chiltern according to 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 of MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at Chiltern.

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 DMP. 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 DMP 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 Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or any other organization contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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 CSP, 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 CSP should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, where relevant, 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. There will also be an optional Genetic consent to be signed if the patient agrees to donate a genetic sample.

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 International co-ordinating Investigator, the Principal Investigators and AstraZeneca.

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

The new version of the CSP 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 CSP to each Principal Investigator. For distribution to Ethics Committee see Section 10.3.

If a change to a CSP 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 CSP, 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.

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Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the subject 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 subject'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).

Hospitalization

Out-subject 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 subject 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, hospitalization, disability or incapacity but may jeopardize the subject 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 hospitalization

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 subject 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 subject 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 Genetic Research

Rationale and Objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

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

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the CSP **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Sections 3.9 to 3.11 of the main CSP.

Collection of samples for genetic research

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

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main CSP.

Informed consent

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

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

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

Appendix D 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 subject meets potential PHL criteria at any point during the study.

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

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

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

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

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 subject 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 subject 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 subject does not meet PHL criteria the Investigator will:

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

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition.

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

    - Subsequent to this contact the Investigator will:

        - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
        - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
        - Complete the three Liver CRF Modules as information becomes available.

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

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

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