TITLE PAGE

Division: Worldwide Development

Title:	A Clinical Outcomes Study to Compare the Incidence of Major Adverse Cardiovascular Events in Subjects Presenting with Acute Coronary Syndrome Treated with Losmapimod Compared to Placebo (PM1116197) **(**Short title: **L**osm**A**pimod **T**o **I**nhibit p38 MAP kinase as a **T**herape**U**tic target and mo**D**ify outcomes after an acute coronary syndrom**E (LATITUDE)-TIMI 60**

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct at my study center. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

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LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACS	Acute Coronary Syndrome
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ARB	ACEi/Angiotensin II Receptor Blocker
ASK1	Apoptosis Signalling Kinase
AST	Aspartate Aminotransferase
AUC	Area Under Concentration-Time Curve
β-HCG	Beta-Human Chorionic Gonadotropin
BID	Twice Daily
BNP	B-Type Natriuretic Peptide
BP	Blood Pressure
BCRP	Breast Cancer Resistance Protein
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum Observed Concentration
CK-MB	Creatine Kinase (MB Isoenzyme)
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRP	C-reactive Protein
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CT	Computed Tomography
CV	Cardiovascular
DDI	Drug Drug Interaction
DRE	Disease Related Event
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
FCBP	Females of Child-Bearing Potential
EQ-5D	EuroQOL Five Dimension Questionnaire
EQ-5D-5L	EuroQOL Five Dimension Questionnaire (Five Level Version)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance

GHO	Global Health Outcomes
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HbA1c	Glycosylated Hemoglobin
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDLc	High Density Lipoprotein Cholesterol
HF	Heart Failure
HIV	Human Immunodeficiency Virus
hsCRP	High-sensitivity C-Reactive Protein
HR	Hazard Ratio
HSP27	Heat Shock Protein 27
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
kg	Kilogram
KLH	Keyhole Limpet Hemocyanin
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDLc	Low Density Lipoprotein Cholesterol
LFTs	Liver Function Tests
LSLV	Last Subject's Last Visit
LT	Liver Test(s)
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LYS	Life Years Saved
µg	Microgram
µL	Microliter
MACE	Major Adverse Cardiovascular Events
MAPK	Mitogen-Activated Protein Kinase
MDRD	Modification of Diet in Renal Disease
MATE	Multidrug and Toxin Extrusion Transporter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams

MI	Myocardial Infarction
mL	Milliliter
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
Msec	Milliseconds
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NOX	Nicotinamide Adenine Dinucleotide Phosphate Oxidase
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
NTproBNP	N-terminal Prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
OAT	Organic Anion Transporter
OCT	Organic Cation Transporter
OD	Once Daily
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic(s)
PI	Principal Investigator
PET	Positron Emission Tomography
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
QALY	Quality-Adjusted Life Years
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SoC	Standard of Care
SOLSTICE	Study Of LoSmapimod Treatment on Inflammation and InfarCt SizE
SOM	Site Operations Manual
SPM	Study Procedures Manual
SRI-UR	Severe recurrent ischemia requiring urgent coronary artery revascularization
STEMI	ST-Segment Elevation Myocardial Infarction
TDAR	T-cell Dependent Antibody Response
TGFβ	Transforming Growth Factor Beta
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TNFα	Tumor Necrosis Factor Alpha
UA	Unstable Angina
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHF	World Heart Federation
WHO	World Health Organization

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PROTOCOL SUMMARY

Rationale

p38 mitogen-activated protein kinase (MAPK) is an intracellular kinase that functions as an important mediator of the inflammatory signalling cascade that leads to activation of cytokine production during acute coronary syndrome (ACS). Evidence to date suggests that p38 MAPK inhibition may potentially interrupt the inflammatory processes in the vascular wall, thus stabilizing atherosclerotic plaques, and reducing the risk of subsequent plaque rupture.

The safety of losmapimod for 12 weeks, and its effects on systemic inflammation, infarct size and cardiac function, was evaluated in a Phase II, randomized, double-blind, placebo-controlled study in 526 subjects presenting with non-ST-segment elevation myocardial infarction (NSTEMI). Acute increases in inflammatory biomarkers (high sensitivity C-reactive protein [hsCRP] and interleukin [IL]-6) during the in-hospital period were significantly attenuated on losmapimod versus placebo. Although the trial was not powered to assess clinical outcomes, there was a non-significant trend toward lower incidence of major adverse cardiovascular events (MACE) in subjects treated with losmapimod compared to placebo, which was driven by a reduction in myocardial infarction (MI). A subgroup of subjects who underwent cardiac magnetic resonance imaging (MRI) had statistically significant improvements in left ventricular ejection fraction (LVEF) and left ventricular (LV) volumes at Week 12 with losmapimod versus placebo.

This Phase III outcomes trial will compare the effects of losmapimod 7.5 mg twice daily (BID) for 12 weeks versus placebo when added to standard of care on the incidence of MACE in subjects with ACS (NSTEMI and ST-segment elevation myocardial infarction [STEMI]).

Objective(s)

The primary objective is to evaluate the efficacy of oral losmapimod 7.5 mg BID compared to placebo when added to standard of care in subjects with ACS on the time to first occurrence of adjudicated MACE (defined as cardiovascular [CV] death, MI, or severe recurrent ischemia requiring urgent coronary artery revascularization [SRI-UR]) through 12 weeks of therapy.

The principal secondary objective is to evaluate the efficacy of losmapimod on the time to first occurrence of adjudicated CV death or MI.

Additional secondary objectives include evaluating the efficacy of losmapimod on other cardiovascular composite elements or individual endpoints including hospitalization for heart failure, stroke, any unplanned coronary revascularization, individual components of MACE, any rehospitalisation in the first 30 days, stent thrombosis, and all-cause mortality.

The safety objective is to evaluate the effects of losmapimod on the incidence of adverse events (AEs), including SAEs and AEs of special interest, and changes in laboratory, physical exam, and ECG parameters.

Exploratory objectives are to evaluate the pharmacokinetics (PK) and PK/pharmacodynamics (PD) of losmapimod, and the effect of losmapimod on health status. Other (non-coronary) atherothrombotic vascular events will also be captured as an exploratory endpoint. Evaluation of cardiovascular and inflammatory biomarkers and genomics will also be performed.

Study Design

This is a randomized, placebo-controlled, double-blind, parallel-group, multicenter study, which will be conducted in two parts. The trial will include approximately 25,500 subjects presenting with NSTEMI or STEMI. Subjects will be randomized 1:1 to receive either oral losmapimod 7.5mg BID or matching placebo BID for 12 weeks, and will be followed for an additional 12 weeks after completing treatment, for a total study duration of 24 weeks.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure scientific integrity of the data and subject safety, and an independent Clinical Events Committee (CEC) blinded to treatment group will adjudicate outcome events.

This study has two parts (Part A and Part B – see Study Design Schema below).

- Part A: leading cohort of 3,500 subjects will be randomized to provide an initial assessment of safety and exploratory efficacy (~200 reports of primary endpoint events) before progressing to Part B. Efficacy data from Part A of the study will not be used in the primary efficacy analysis of the trial.
- Part B: the main cohort will be event driven with approximately 22,000 subjects randomized to provide the main assessment of efficacy with an event target of 1,400 adjudicated primary endpoint events, and 1,000–1,200 adjudicated CV death/MI.

Part A

Part A is planned to provide an initial evaluation of safety and exploratory efficacy to give confidence before proceeding with the main cohort. It is planned to randomise 3,500 subjects into Part A, which will deliver approximately 200 MACE events. All subjects randomized into Part A are expected to continue the planned follow-up phase to Week 24.

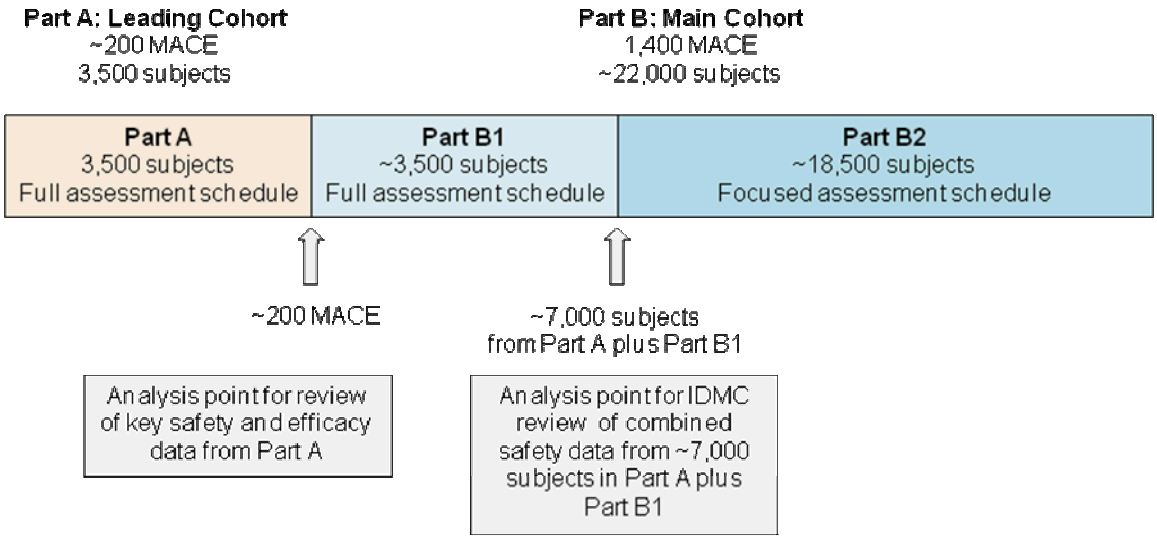
Upon completion of the treatment phase of Part A, summary level unblinded efficacy and safety data from Part A will be reviewed by a limited group involved in study conduct (comprising trial leadership from the Sponsor and TIMI), who will make a decision on whether or not to proceed to Part B. This review will occur prior to initiation of recruitment in Part B. The pivotal analyses of the study will be based on Part B alone, however investigators will remain blinded to subject-level Part A data. A decision to proceed to Part B can only be made with endorsement with respect to safety from the IDMC.

Part B

Part B of the study will be event driven and will provide the main assessment of the efficacy of losmapimod compared to placebo for the treatment of ACS. After the decision is made at the end of Part A to progress the study, enrolment into Part B will commence. After approximately 7,000 patients (3,500 from Part A plus 3,500 from Part B1) have completed treatment, the IDMC will review safety data to make a recommendation on whether a focused schedule of assessments can be followed for subsequent subjects enrolled in Part B2 (replacing a clinic visit with phone contact at Week 4 and Week 24 and reducing the schedule of clinical laboratory tests).

The size of Part B has been determined based on an event target of 1,400 adjudicated primary endpoint events. It is anticipated that approximately 22,000 subjects will be recruited to achieve this event target. The primary inference for efficacy will be based on the assessment of data from Part B. The primary inference for safety will be based on the assessment of the combined safety database from both cohorts (Part A and Part B).

Two Part Study Design (Study Design Schema)



Study Endpoints/Assessments

Primary Endpoint: The primary efficacy endpoint is the composite of adjudicated MACE that includes the time to first occurrence of CV death, MI, or SRI-UR. If the effect of losmapimod on MACE shows a statistically significant benefit over placebo, then the analysis will proceed to testing the hypothesis for the principal secondary endpoint using a serial gate keeping procedure to account for multiplicity.

Principal Secondary Endpoint: The principal secondary endpoint is the time to first occurrence of the composite of adjudicated CV death or MI.

Additional events that will comprise other secondary composite elements or endpoints include: hospitalization for heart failure, all coronary revascularization (other than planned for the qualifying event), stroke, coronary heart disease death, all-cause mortality, stent thrombosis, and rehospitalization within 30 days of discharge. Other (non-coronary) atherothrombotic vascular events will be captured as an exploratory endpoint.

All primary endpoint and principal secondary endpoint events, as well as hospitalization for heart failure, stroke, stent thrombosis, and coronary heart disease death, will be adjudicated by an independent CEC blinded to treatment.

In addition to the assessment of clinical outcomes, health status will be assessed at hospital discharge, at the end of treatment, and at the end of the study in a subset of subjects, according to the Time and Events tables.

Blood samples will also be collected, according to the Time and Events tables, at various timepoints for assay of circulating biomarkers of CV risk and inflammation, genetic and pharmacokinetic analyses.

1. INTRODUCTION

1.1. Background

Acute Coronary Syndrome and the Role of Inflammation

Acute coronary syndrome (ACS), comprised of non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI) and unstable angina (UA), is associated with significant risk for subsequent cardiovascular death, and recurrent ischemic events, including myocardial infarction. The period of highest risk for recurrent ischemic events is within 3 months after the index event. The majority of recent therapeutic advances in ACS have been achieved by targeting the thrombotic component of the ACS process. However, despite treatment of the thrombus through a variety of mechanisms, the rate of ACS and its sequelae remains unacceptably high, with rising global incidence [Lloyd-Jones, 2010]. Additionally, the use of increasingly potent anti-thrombotic agents has been associated with an increased risk of bleeding, potentially limiting the net clinical benefit of these agents.

Angiographic and vascular biomarker studies have found both a high incidence of early non-culprit lesion progression, often resulting in recurrent unstable ischemic events, as well as the presence of inflammatory cells across the coronary vascular bed [Goldstein, 2000; Glaser, 2005; Buffon, 2002]. Vulnerable plaques, in patients with ACS are associated with systemic markers of inflammation [Buja, 1994], such as C-reactive protein (CRP) [Morrow, 1998; Scirica, 2007], which is a significant predictor of later ischemic events. Additional inflammatory biomarkers, such as serum amyloid A, interleukin (IL)-6 and IL-1 receptors have emerged as either acutely or chronically predictive of subsequent adverse cardiac events in patients with coronary disease. Further, it has been suggested that these markers may represent not only a reflection of necrosis and reperfusion injury, but also primary causal agents in the cascade leading to ACS [Libby, 2002]. Accordingly, novel strategies to reduce the acute inflammatory state associated with ACS may provide important future therapeutic advances.

p38 Mitogen-Activated Protein Kinase as a Therapeutic Target in ACS

p38 mitogen-activated protein kinase (MAPK) is an intracellular kinase that functions as an important mediator of the inflammatory signalling cascade that leads to activation of cytokine production during ACS. This kinase is expressed in vascular endothelium, smooth muscle, macrophages that invade atherosclerotic plaques, and in cardiac myocytes, and it is activated in response to stress mediators including hypertension, oxidized low density lipoprotein cholesterol (LDLc), ischemia, and vascular injury [Marber, 2011]. Activation of p38 MAPK [Hommes, 2003] subsequently leads to expression of tumor necrosis factor alpha (TNFα), interleukin (IL)-1, IL-6, cyclo-oxygenase 2 and metalloproteinases [Schett , 2008]. In turn, CRP production in the liver is upregulated by p38 MAPK-dependent cytokines such as IL-1 and IL-6.

Losmapimod (GW856553)

Losmapimod is a novel, selective, reversible, orally administered inhibitor of p38 MAPK α and β. Refer to the Investigator's Brochure for further information (see Study Procedures Manual [SPM] for current version of the Investigator's Brochure).

There are several key biological functions of p38 MAPK in the coronary vessel wall and in the myocardium demonstrated in both preclinical animal models and human studies, which make p38 MAPK inhibition a potentially important therapeutic approach in ACS. Activated macrophages in atherosclerotic plaques are involved in plaque destabilization and release of inflammatory cytokines, causing an increase in overall inflammatory activation of subsequent plaques, and vasoconstriction. Preclinical and clinical studies have demonstrated improved vasoregulatory function with p38 MAPK inhibition [Ju, 2003] and improvements in endothelial-independent forearm blood flow in dyslipidemic patients [Cheriyan, 2011]. A reduction in vascular inflammatory activity has been shown following treatment with losmapimod in patients with atherosclerosis on stable statin therapy, as evidenced by cellular uptake of ^{18}F-fluorodeoxyglucose measured by positron emission tomography (PET)/computed tomography (CT) [Elkhawad, 2012]. In two separate clinical studies, post-percutaneous coronary intervention (PCI) inflammatory responses (evidenced by CRP) were reduced in patients treated with a p38 MAPK inhibitor (SB-681323 and VX-702, respectively), compared to standard of care treatments which included statin use [Sarov-Blat , 2010; Ding, 2006].

Losmapimod was evaluated for 12 weeks in a randomized, double-blind, placebo-controlled study in 526 patients presenting with NSTEMI (PM1111810). Acute increases in inflammatory biomarkers (high sensitivity C-reactive protein [hsCRP] and IL-6) during the in-hospital period were significantly attenuated on losmapimod versus placebo. Although the trial was not powered to assess clinical outcomes, there was a non-significant trend toward lower incidence of major adverse cardiovascular events (MACE) in subjects treated with losmapimod compared to placebo, which was driven by a reduction in myocardial infarction (MI). A subgroup of subjects who underwent cardiac magnetic resonance imaging (MRI) had statistically significant improvements in left ventricular ejection fraction (LVEF) and left ventricular (LV) volumes at Week 12 with losmapimod versus placebo.

Evidence to date suggests that p38 MAPK inhibition may potentially attenuate the inflammatory processes in the vascular wall, stabilizing atherosclerotic plaques, and reducing the risk of subsequent plaque rupture.

1.2. Rationale

Based on the role of p38 MAPK in the mediation of inflammatory events associated with ACS, it is postulated that inhibition of this enzyme may provide therapeutic benefits in patients presenting with ACS.

This Phase III outcomes trial will compare the effects of losmapimod 7.5 mg twice daily (BID) for 12 weeks versus placebo when added to standard of care on the incidence of MACE in subjects with ACS (NSTEMI and STEMI). This study has two parts: the first is a leading cohort (Part A) and the second, a larger main cohort (Part B). The leading

cohort is planned to provide an initial evaluation of safety and exploratory efficacy to give confidence before proceeding with the main cohort.

Summaries of findings from both clinical and non-clinical studies conducted with losmapimod can be found in the Investigator Brochure (IB) [GlaxoSmithKline Document Number WM2004/00033/09]. The following section outlines the risk assessment and mitigation strategy for this protocol.

1.2.1. Benefit Assessment

Despite available treatments, ACS patients are still at significant risk for recurring CV events such as CV related death, MI, and stroke. The anticipated benefits of losmapimod, which has a novel anti-inflammatory mechanism of action, is to significantly reduce MACE, including cardiovascular death, MI and severe ischemia. Losmapimod may improve cardiovascular outcomes without an increase in risk of bleeding, as losmapimod has no known influence on platelets or coagulation factors, and without compromising the ability to administer other cardiovascular therapies which constitute the standard of care for ACS patients.

1.2.2. Risk Assessment

Hepatotoxicity

In clinical trials to date, elevations in transaminases have occurred in few subjects among over 1,500 exposures of losmapimod. These have generally been mild, asymptomatic, and reversible, and the majority were confounded by other medications or clinical conditions (Details reported in IB). Preclinical data demonstrate reversible increases in rat liver weight with no clinical chemistry or microscopic correlate (Details reported in IB). However, hepatotoxicity has been observed after repeat dose administration of some previous p38 MAPK inhibitors. The mechanism of heptatoxicity for those compounds has not been elucidated and thus applicability to losmapimod is unknown. Exclusion criteria (Protocol Section 4.3), data collection, and Investigational Product [IP] stopping criteria (Protocol Section 6.4.1 and Appendix 3) relating to liver chemistries are well defined.

Embryo-fetal Malformations

Embryo-fetal malformations in rats and rabbits have been observed with losmapimod (Details reported in IB). IP will not be administered to women of childbearing potential unless they are employing adequate contraceptive measures (Protocol Section 4.2). Pregnancy testing is required at baseline and at the time points specified in Protocol Time and Events Schedule (Table 1) during the treatment period. Unexpected pregnancies will be reported with instructions for appropriate follow up (Protocol Section 6.4.8).

Drug Drug Interaction (DDI)

Losmapimod is considered unlikely to have a clinically relevant DDI with substrates or inhibitors of cytochrome P450, P-gp, human organic anion transporting polypeptides 1B1 and 1B3, human organic anion transporters (OAT) or human renal cation transporter

(OCT) 2 (Details reported in IB). Losmapimod inhibits multidrug and toxin extrusion (MATE) 1 and MATE2-K renal transporters *in vitro* with a low risk of clinically relevant interaction.

Both losmapimod and its major metabolite, GSK198602, are *in vitro* inhibitors of human breast cancer resistance protein (BCRP) (See IB). In the case of co-administration of IP with orally administered BCRP substrates with a narrow therapeutic index, careful monitoring for adverse effects of these agents is advised (Protocol Section 5.6.2).

Infection/Immunity

Based on its pharmacology, losmapimod has a modest but broad inhibitory influence on various inflammatory cytokines. Thus, losmapimod may theoretically have an impact on immunity, and be associated with an increased risk of infection. Incidence of infections to date has been similar in losmapimod versus placebo in controlled studies (See IB).

Preclinical rat studies demonstrated marked reductions in IgM and IgG responses in a T cell-dependent antibody response (TDAR) study when administered at *near maximal* inhibition doses. These findings were reversible following a 4-week recovery period (See IB).

Subjects receiving cytotoxic therapy for the treatment of cancer, subjects receiving or anticipated to receive severe immunosuppressive agents, and subjects with known active tuberculosis, and active opportunistic or life-threatening infections at the time of screening are excluded (Protocol Section 4.3). Information for all infections identified as serious adverse events will be collected (Protocol Section 6.4.6).

Subjects who have received attenuated live vaccines within 6 weeks prior to randomization will be excluded (Protocol Section 4.3). Attenuated live vaccines should not be administered during dosing of IP and for the period 4 weeks after treatment (Protocol Section 5.6.2).

Renal Function

In clinical studies, a small asymptomatic increase in serum creatinine with losmapimod of 1 to 7% was noted; this increase appeared to attenuate with continued therapy as well as with discontinuation (See IB). In addition, an exploratory analysis of cystatin levels was performed in the PM1111810 trial to determine if the observed increase in creatinine reflected a decrease in glomerular filtration. There was not a significant increase of cystatin in the losmapimod group compared to placebo at week 12 compared to baseline (risk ratio of 1.03 [95% CI: 0.97, 1.08]).

Renal function (Protocol Section 6.4.15) and AEs will be monitored during the trial.

1.2.3. Overall Benefit:Risk Conclusion

In clinical trials to date, no serious safety risks clearly attributable to losmapimod have been identified. Losmapimod has demonstrated meaningful pharmacological activity in the ACS clinical trial population, and has not demonstrated significant safety or tolerability issues in any of the populations studied. Available evidence shows losmapimod to have a potentially favorable benefit:risk profile.

2. OBJECTIVE(S)

2.1. Primary Objective

The primary objective is to evaluate the efficacy of oral losmapimod 7.5 mg BID compared to placebo when added to standard of care in subjects with ACS on the time to first occurrence of adjudicated MACE (defined as CV death, MI, or severe recurrent ischemia [SRI-UR]) through 12 weeks of therapy.

2.2. Secondary Objectives

Principal Secondary Objective

The principal secondary objective is to evaluate the efficacy of losmapimod on the time to first occurrence of adjudicated CV death or MI.

Additional Secondary Objectives

Additional secondary objectives are to evaluate the efficacy of losmapimod on the time to first occurrence of:

- The composite of CV death, MI, or hospitalization for heart failure (HF).
- The expanded composite of arterial CV events, defined as CV death, MI, SRI-UR, or stroke.
- The composite of coronary events (defined as CHD death, MI, SRI-UR, or any unplanned coronary artery revascularization).

  Planned coronary artery revascularizations are those initial or staged interventions performed based on the initial qualifying ACS.
- The composite of CV death or hospitalization for HF
- The composite of CV death, MI or stroke.
- The composite of CV death, MI, SRI-UR, stroke or hospitalisation for HF
- The primary and principal secondary endpoints will be evaluated replacing CV death separately with CHD death ("Coronary MACE") and all-cause death.
- The primary and principal secondary endpoints will be evaluated replacing all MI with Type 1 (spontaneous) MI.
- Individual components of the composite endpoints (including all-cause mortality).
- Definite or probable stent thrombosis.
- Any re-hospitalization within 30 days of discharge.

For the primary and each of the secondary endpoints, the principal analysis will be through 12 weeks, with additional analyses through 4 and 24 weeks unless otherwise stated. In addition, a recurrent event analysis (i.e. accounting for subjects who experience

multiple events) will be conducted for each composite endpoint. Additional endpoints will be specified in the Reporting and Analysis Plan (RAP).

All outcome events as specified in section 6.3 will be adjudicated by an independent Clinical Events Committee (CEC) blinded to treatment.

2.3. Safety Objective

The safety objective is to evaluate the effects of losmapimod on the incidence of adverse events (AEs), including SAEs, AEs of special interest, and changes in laboratory, physical exam, and ECG parameters.

2.4. Exploratory Objectives

Exploratory objectives are to evaluate the pharmacokinetics (PK) and PK/pharmacodynamics (PD) of losmapimod, and the effect of losmapimod on health status in subsets of subjects according to the Time and Events tables. Other (non-coronary) atherothrombotic vascular events will also be captured as an exploratory endpoint. Evaluation of genomics and cardiovascular and inflammatory biomarkers are described in Appendix 4 and Appendix 5, respectively.

3. INVESTIGATIONAL PLAN

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Protocol waivers or exemptions are not allowed with the exception of managing immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, is essential and required for study conduct.

3.1. Study Design

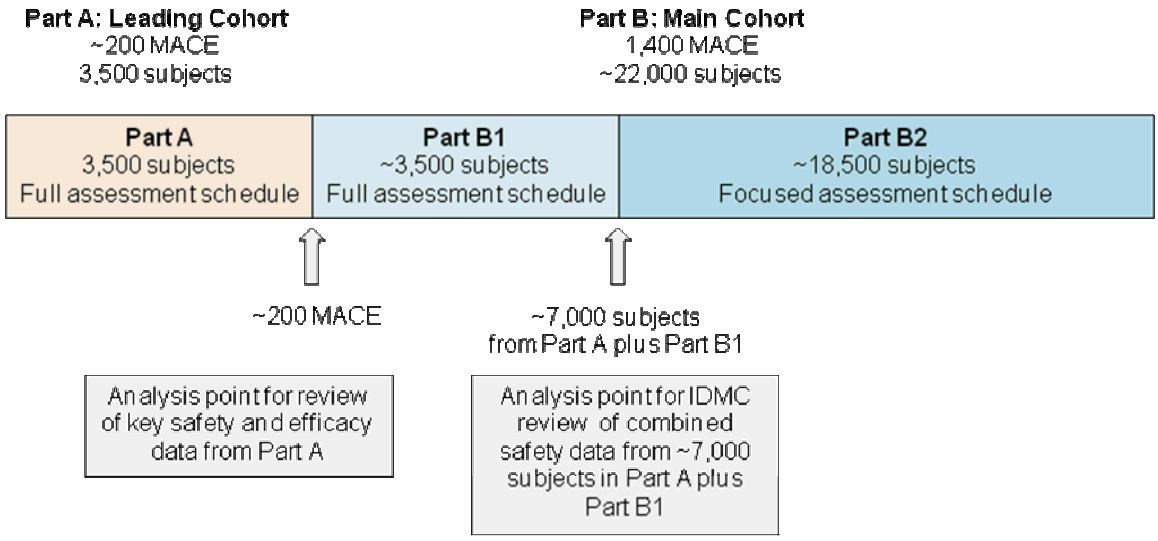
This is a randomized, placebo-controlled, double-blind, parallel-group, multicenter study which will be conducted in two parts (Figure 1). The trial will include approximately 25,500 subjects presenting with NSTEMI or STEMI. Subjects will be randomized 1:1 to receive either oral losmapimod 7.5mg BID or matching placebo BID for 12 weeks in addition to standard of care, and will be followed for an additional 12 weeks after completing treatment, for a total study duration of 24 weeks.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure scientific integrity of the data and subject safety, and an independent CEC blinded to treatment will adjudicate outcome events.

This study has two parts (Part A and Part B).

- Part A: leading cohort of 3,500 subjects will be randomized to provide an initial assessment of safety and exploratory efficacy (~200 adjudicated + pending primary endpoint events) before progressing to Part B. Efficacy data from this stage of the study will not be used in the primary efficacy analysis of the trial.
- Part B: the main cohort will be event driven with approximately 22,000 subjects randomized to provide the main assessment of efficacy with an event target of 1,400 adjudicated primary endpoint events, and 1,000–1,200 adjudicated CV death and MI events.

Figure 1 Two Part Study Design



Composite of adjudicated MACE (major adverse cardiovascular events) defined as cardiovascular death, myocardial infarction, or severe recurrent ischemia requiring urgent coronary artery revascularization.

3.1.1. Part A

Part A is planned to provide an initial evaluation of safety and exploratory efficacy to give confidence before proceeding with the main cohort. It is planned to randomise 3,500 subjects into Part A, which will deliver approximately 200 MACE events. All subjects randomized into Part A are expected to continue the planned follow-up phase to Week 24.

Upon completion of the treatment phase of Part A, summary level unblinded efficacy and safety data from Part A will be reviewed by a limited group involved in study conduct (comprising trial leadership from the Sponsor and TIMI), who will make a decision on whether or not to proceed to Part B. This review will occur prior to initiation of recruitment in Part B. The pivotal analyses of the study will be based on Part B alone, however investigators will remain blinded to subject-level Part A data. A decision to proceed to Part B can only be made with endorsement with respect to safety from the IDMC.

3.1.2. Part B

Part B of the study will be event driven and will provide the main assessment of the efficacy of losmapimod compared to placebo for the treatment of ACS. After the decision is made at the end of Part A to progress the study, enrolment into Part B will commence. After approximately 7,000 patients (3,500 from Part A plus 3,500 from Part B1) have completed treatment, the IDMC will review safety data to make a recommendation on whether a focused schedule of assessments can be followed for subsequent subjects enrolled in Part B2 (replacing a clinic visit with phone contact at Week 4 and Week 24 and reducing the schedule of clinical laboratory tests).

The size of Part B has been determined based on an event target of 1,400 adjudicated primary endpoint events. It is anticipated that approximately 22,000 subjects will be recruited to achieve this event target. The primary inference for efficacy will be based on the assessment of data from Part B. The primary inference for safety will be based on the assessment of the combined safety database from both cohorts (Part A and Part B).

3.1.3. Screening Phase

The screening process may begin after a subject presents with signs and symptoms consistent with ACS (NSTEMI or STEMI).

Written informed consent must be obtained from each subject prior to undergoing any study-specific procedures. Subjects may be eligible for this study regardless of whether early invasive or conservative management is planned; however, it is expected that the majority of patients will undergo invasive evaluation for high risk ACS, including subjects with STEMI initially treated with fibrinolysis. Subjects who are to undergo coronary revascularisation for the qualifying event should be randomised and start treatment with IP prior to the procedure. In addition, subjects with STEMI who are to be treated with fibrinolysis must take at least one dose of IP prior to initiation of the fibrinolytic.

Each subject will be treated at the discretion of his/her treating physician according to the standard of care for ACS during in-hospital treatment and after hospital discharge consistent with the appropriate guidelines from professional societies [Anderson, 2013, O'Connor, 2010; O'Gara , 2013, Smith, 2011;; Hamm, 2011; Steg, 2012]. A screening log electronic case report form (eCRF) must be completed for every subject with a signed informed consent form (ICF). The reason for screen failure will be documented in a Screening Log maintained at the investigational site. Reasons for screen failure will also be collected in the electronic screening log.

The following procedures must be completed to ensure that the subject is eligible for the study:

- Obtain informed written consent
- Review inclusion/exclusion criteria, including concomitant medications.

Full source documentation for the above qualifying procedures and related results are required even if local laboratory results were used to qualify the subject.

It is anticipated that some subjects will have some or all of the study qualification procedures done as part of routine care outside the auspices of this study. As long as these procedures, including local laboratory tests, were obtained during transport to the hospital or after arrival with the qualifying MI and before randomization, the results of these procedures may be used to complete the screening log eCRF.

Any protocol-specified study qualification procedures not already done as part of routine care will need to be conducted after the subject signs the ICF and before randomization.

The results of all study qualification procedures, whether performed as part of routine care or as a study specific procedure, are required to assess subject inclusion/exclusion criteria and should, if possible, be available prior to randomization. Local laboratory results should be assessed against the exclusion criteria to determine subject eligibility. Those samples taken prior to or at the time of randomization and sent to the central laboratory will serve as the baseline for assessment of the treatment effect (see Time and Events Tables in Section 6).

If local laboratory results are not already available prior to randomization, a sample must be obtained at the time of randomization and sent to the local laboratory for evaluation of liver chemistries and serum creatinine to calculate estimated glomerular filtration rate (eGFR). IP can be started before the results of these local laboratory tests are known. For such local laboratory results obtained at randomization (with results known only after randomization) apply the following:

- If ALT ≥2xULN or bilirubin >1.5xULN then follow the procedures in Section 6.4.1.
- If eGFR is less than 30ml/min/1.73m^2 then consult with the GSK medical monitor/TIMI Hotline.

The screening process ends when randomization occurs. For NSTEMI, randomization must occur within 24 hours of the most recent ischemic symptoms lasting ≥5 min at rest. For STEMI, randomization must occur within 12 hours of symptom onset for the qualifying event.

3.1.4. Treatment Phase

The Treatment Phase begins at randomization.

In-hospital Period

In both Parts A and B, subjects who are eligible for the study will be randomized 1:1 to receive oral losmapimod 7.5 mg BID or matching placebo (referred to as investigational product [IP]) for 12 weeks (+2 weeks). Separate randomization schedules will be generated for Part A and Part B.

It is anticipated that the majority of the total study population will undergo coronary revascularization (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) for the qualifying event, consistent with current therapeutic guidelines for high risk ACS patients. Invasive evaluation is not mandated to qualify for the study, but if a subject is to undergo coronary revascularization for the qualifying

event, randomization and administration of the first dose of IP must occur prior to revascularization. If a subject has undergone coronary revascularization for the qualifying event prior to randomization, he/she is no longer eligible for the trial, even if additional PCI procedures are planned.

Analogously, for subjects with STEMI undergoing fibrinolysis, subjects must be randomized and administered the first dose of IP prior to administering any fibrinolytic treatment. If a subject has received a fibrinolytic for the qualifying MI prior to randomization, he/she is no longer eligible for the trial. It is anticipated that most subjects undergoing fibrinolysis will be referred for coronary angiography, ideally between 3 to 24 hours after fibrinolytic administration.

IP should be administered within 2 hours after randomization, and prior to starting any coronary revascularization procedure or fibrinolytic administration for the qualifying event.

Subjects will be followed throughout their hospitalization with a pre-discharge assessment for potential endpoints and adverse events (Table 1). Subjects who are transferred from the enrolling study center to another hospital for continued care should continue IP and study procedures according to the protocol. For subjects transferred to a hospital not participating in the study, study procedures should be conducted, whenever possible.

After Hospital Discharge

During the Treatment Phase, subjects will return for scheduled clinic visits at Week 4 (±2 weeks), the End of Treatment Visit at Week 12 (+2 weeks), and at the end of the study at Week 24 (±2 weeks,). The End of Treatment Visit should be performed no earlier than 12 weeks (84 days) after randomization. After IDMC assessment of safety data from Part A plus Part B1, the schedule of visits and procedures may be modified in Part B2, such that the Week 4 and Week 24 visits will be performed by phone call, as specified in Section 3.1.2 and Table 1. Participating study sites will be notified if and when the focused schedule of assessments can be adopted for the remainder of the trial.

At each visit, the investigator (or qualified designee) will evaluate the subject's health status in accordance with the current professional society guidelines and standard of care for management of ACS. If a subject permanently discontinues treatment with IP prior to the end of the planned treatment phase, then the subject will be asked to return to the clinic for an IP Early Discontinuation Visit (see Section 4.4, and Table 1) and subsequently continue follow-up according to the visit schedule, including the Week 12 clinic visit (Table 1). Subjects who have prematurely discontinued IP and are unable to perform in-person visits according to the visit schedule will be followed by telephone or other means, unless consent for all forms of contact is specifically withdrawn. Refer to Section 4.5 for the importance of subject followup and additional instructions. An unscheduled clinic visit or telephone contact may occur at any time at the subject's request or if the investigator believes an unscheduled visit is clinically warranted.

Subjects who experience any clinical event constituting a potential endpoint during the 12-week treatment period should continue treatment with IP as planned.

The selection of individual concomitant medications, dosages, or titration schemes is left to the discretion of the investigator, although it is strongly recommended that treatments conform to the standard of care recommended in professional society guidelines. During the study, investigators will be provided with updates at regular intervals that summarize adherence to guideline-mandated recommended therapies.

Follow-up Phase

Follow-up contact will be made with each subject at Week 24 (±2 weeks) to collect endpoint, adverse event information, and laboratory data, according to the Time and Events Schedule (Table 1). The total duration of each subject's participation in the study will be approximately 24 weeks.

All subjects will be followed until completion of 24 weeks from the time of randomization, regardless of whether they permanently discontinue IP or experience a non-fatal clinical event constituting an endpoint. Every reasonable effort will be made to keep the number of subjects who withdraw from follow-up in the study to a minimum. Retention of subjects in the study will be encouraged and monitored by the study team.

3.2. Discussion of Design

3.2.1. Study Design

This study is a clinical outcomes trial. It will provide important information regarding the therapeutic role of short-term (12-week) losmapimod treatment of ACS through the novel mechanism of p38 MAPK inhibition when added to standard of care. Subjects will be randomized and receive the first dose of IP before undergoing any coronary revascularization or fibrinolytic therapy for the qualifying ACS to optimize any potential anti-inflammatory benefit in the peri-revascularization/reperfusion period. The treatment duration of 12 weeks is anticipated to be sufficient to allow attenuation of inflammation during the acute cardiovascular healing period.

This will be a double-blind, placebo-controlled study. All subjects will receive placebo or losmapimod in addition to usual standard of care for ACS, in order to assess the effect of losmapimod above that of currently available therapies alone.

This study has an operationally seamless design to be conducted in two stages that are described in Section 3.1 (Figure 1). Primary efficacy analyses for the study as a whole will be based on Part B. The primary analyses for safety will be based on an assessment of the combined safety database from Part A and Part B.

The primary clinical endpoint selected for this study, MACE (defined as CV death, MI or SRI-UR) is an established cardiovascular endpoint and losmapimod is believed to have a vascular benefit. An external IDMC will monitor safety in the study and an independent CEC will review and adjudicate all clinical events that may constitute MACE or other selected key endpoints.

The post-treatment follow-up period will enable examination of maintenance of efficacy and additional assessment of safety.

3.2.2. Dose Rationale

The goal of dose selection with losmapimod is to reach sub-maximal inhibition of p38 MAPK, aiming to achieve a resultant reduction in the risk of MACE, while maintaining an acceptable safety and tolerability profile. The losmapimod 7.5 mg BID dose for this study was chosen on the basis of the PK, PD and safety profiles of losmapimod observed in Phase I and II studies summarized below. Refer to the Investigator's Brochure for further information on losmapimod.

Pharmacodynamic Effects

Heat shock protein 27 (HSP27) is a representative component of the p38 MAPK signaling pathway, and its activation, via phosphorylation, is directly related to the activity of p38 MAPK.. When tested *ex vivo* under stressor conditions, e.g. sorbitol treatment, attenuated HSP27 phosphorylation/ activation correlates well with the degree of p38 MAPK inhibition [Xu, 2006]. A 2.5 mg BID dose provides about half the inhibition of 7.5mg BID dosing, and conversely, a 15 mg BID dose provides approximately 12% additional inhibition of 7.5 mg BID, suggesting diminishing improvements in terms of the risk/benefit ratio with increased doses.

CRP is a biomarker of systemic inflammation and elevated levels are associated with an increased risk of mortality in patients with ACS [Morrow, 1998; Scirica, 2007]. In a dose-ranging study in subjects with chronic obstructive pulmonary disease (COPD) (Study MKI113006), the 2.5 mg BID dose did not provide the desired reduction in markers of inflammation. The effect of the 2.5 mg BID dose on hs-CRP was indistinguishable from placebo. Although 15 mg BID is projected to inhibit p38 MAPK to a greater degree than 7.5 mg BID, 15 mg BID does not translate into a further attenuation of the inflammatory process. In the same COPD study, both 7.5 mg BID and 15 mg BID reduced hs-CRP significantly and to largely the same extent. There is reason to believe that inferences about the dose-response relationship in the COPD population can be extrapolated to cardiovascular disease patients, as similar reductions of hs-CRP from baseline compared to placebo were observed between the two populations.

Clinical Efficacy in Subjects with Cardiovascular Disease at a Dose of 7.5 mg BID

With regard to efficacy in CV disease, losmapimod 7.5 mg BID compared to placebo has been associated with:

- Improvement in endothelium-independent vasodilation and a trend towards improvement in endothelium-dependent vasodilatation in dyslipidemic subjects.
- A decrease in *in vivo* macrophage activity as measured by the proportion of active segments shown on ^{18}F-fluorodeoxyglucose PET/CT imaging of the carotid arteries or aorta of subjects with atherosclerosis.
- Attenuation of the rise in inflammatory biomarkers during the in-hospital period in subjects with NSTEMI.
- A lower B-type natriuretic peptide (BNP) level compared with placebo following 12 weeks of treatment in subjects with NSTEMI.

- Higher left ventricular ejection fraction (LVEF) at 12 weeks in patients with NSTEMI as compared to placebo and a non-significant reduction in infarct size, both measured by MRI. These findings are supported by an exposure/response analysis.
- A hazard ratio for first occurrence of MACE (defined as all-cause death, adjudicated MI or stroke), comparing losmapimod to placebo, of 0.86 (95% CI 0.49, 1.51) in patients with NSTEMI.

Dosing Interval

PK/PD modelling and simulation of the inhibition of phosphorylation of HSP27 predicted a greater response at trough losmapimod concentrations for 7.5 mg BID (~28% inhibition from baseline) compared to 15 mg once daily (OD) (~16% inhibition from baseline). The twice daily regimen has been selected to maintain the higher level of inhibition throughout the dosing interval. It also significantly reduces the peak drug concentration and thereby reduces the potential for concentration-related adverse effects.

Dosing Duration of 12 Weeks

The period of highest risk for recurrent ischemic events is within 3 months after the index event and is associated with elevated inflammation [Wallentin, 2009; Wiviott, 2006]. Events from 15 days to 6 months post-ACS continue to substantially supersede the incidence in chronic atherosclerosis, e.g,. 6% in that period compared to the same rate in chronic atherosclerosis over 2-4 years [Yusuf, 2003]. This suggests a continuing inflammatory setting prompting further plaque ruptures [Maseri, 2003]. In NSTEMI patients, losmapimod administered within a median of 12 hours from admission significantly reduced CRP and this reduction was still evident 2 weeks later. Over a period when myocardial healing takes place, BNP was found to be significantly lower in patients treated with losmapimod compared with placebo by the end of the 12-week dosing period. Thus, 3-month duration of therapy for losmapimod provides the best opportunity to reduce the heightened risk of recurrent events secondary to the inflammatory burst of activity surrounding ACS and consequent plaque rupture, while minimizing the duration of therapy.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

The trial will include approximately 25,500 patients presenting with NSTEMI or STEMI.

- Part A: leading cohort of approximately 3,500 subjects will be randomized to provide an initial assessment of safety and exploratory efficacy (~200 reports of MACE) before progressing to Part B.

- Part B: the main cohort will be event driven with approximately 22,000 subjects randomized to provide the assessment of efficacy with an event target of 1,400 adjudicated primary endpoint events. and 1,000–1,200 adjudicated CV death/MI.

During the recruitment period, the distribution of NSTEMI and STEMI subjects, and use of fibrinolytic therapy, will be monitored, and enrollment of subjects with one type of ACS may be closed if deemed appropriate.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator Brochure for losmapimod.

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

If it is found that a randomized subject did not meet all eligibility criteria, that subject may be allowed to continue IP unless continuation presents a concern for the subject's safety. The GSK study monitor/TIMI Medical Hotline should be contacted whenever it is discovered that a randomized subject did not meet all eligibility criteria.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Signed written informed consent prior to beginning study-related procedures.

   The subject must understand the aims, investigational procedures and possible consequences of the study

2. Male or female aged 35 years or older at randomization.

   A female subject is eligible to participate if she is of non-child bearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea or if of child-bearing potential is using a highly effective method for avoidance of pregnancy (refer to Appendix 1) for the duration of dosing and until 2 weeks post last-dose. The decision to include or exclude women of childbearing potential may be made at the discretion of the investigator and in accordance with local practice in relation to adequate contraception.

3. Hospitalization for NSTEMI or STEMI (Universal Definition Type 1 MI).

   NSTEMI *that is presumed spontaneous (Universal Definition Type 1) and is defined as ischemic chest discomfort (or equivalent) that occurs or persists at rest with at least 1 episode lasting ≥10 minutes and is accompanied by a diagnostic elevation in cardiac troponin above the upper limit of normal (99th percentile decision-limit) according to the local laboratory without persistent ST segment elevation. If cardiac troponin is not available, then creatine-kinase MB isoenzyme (CK-MB) must be above the upper limit of normal. The biomarker should exhibit a rising and/or falling pattern when serial testing is available prior to randomization.*

   STEMI *is defined as ischemic chest discomfort (or equivalent) that occurs or persists at rest with ST segment elevation of at least 0.1 mV in 2 or more contiguous leads or new (or presumed new) left bundle branch block (LBBB) and a presumed diagnosis of STEMI.*

NOTE: *Subjects with clinical or laboratory manifestations of ACS (e.g., ST-elevation or increase in cardiac enzymes) that are believed to be secondary to other apparent illness (e.g., sepsis, profound anemia, hypertensive emergency or decompensated heart failure, coronary embolism or dissection; Universal Type 2 MI) or known to be procedurally related (Type 4 - including stent thrombosis- or Type 5) are* ***not*** *considered to meet these criteria for NSTEMI or STEMI.*

4. With the following timing of symptoms:

   NSTEMI: Presence of ischemic symptoms (≥5 minutes) at rest within 24 hours prior to randomization (may include qualifying episode).

   STEMI: Onset of qualifying ischemic symptoms within 12 hours of randomization.

5. All subjects must also have at least one of the following additional predictors of cardiovascular risk:

   a. Age ≥60 years at randomization.

   b. History of documented MI (known or presumed Type 1 MI) prior to qualifying ACS event.

   c. History of CABG prior to qualifying ACS event.

   d. NSTEMI with new ischemic ST-segment depression ≥0.1 mV in ≥2 contiguous leads.

   e. Diabetes mellitus requiring pharmacotherapy.

   f. Coexistent clinically diagnosed arterial disease in at least 1 peripheral arterial territory, defined as:

      - History of non-cardioembolic (known or presumed), ischemic stroke (confirmed by medical records or history) or
      - Current or history of peripheral arterial disease: current intermittent claudication with an ankle-brachial index ≤0.85 or history of peripheral arterial stenting or surgery (including amputation due to vascular causes).

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

If it is found that a randomised subject did meet an exclusion criteria, that subject may be allowed to continue IP unless continuation presents a concern for the subject's safety. The GSK study monitor/TIMI Medical Hotline should be contacted whenever it is discovered that a randomised subject met any exclusion criteria.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Unable to be randomized prior to coronary revascularization or fibrinolysis for the qualifying MI.
2. Current severe heart failure or shock (New York Heart Association [NYHA] class III or IV, or Killip class III or IV).
3. Ongoing clinical instability (e.g., hypotension requiring vasopressor or inotropic support, new stroke or transient ischemic attack [TIA], or recurrent sustained ventricular tachycardia).
4. History of chronic liver disease (defined below) or known to have current ALT ≥2x upper limit of normal or total bilirubin >1.5x upper limit of normal or known history of hepatitis B or C.

   Defined as known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Such abnormalities include current drug therapy for the treatment of liver disease, unstable liver disease (defined by the presence of any of the following deemed by the investigator to be related to liver disease and not to other disease processes: ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice) or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study.
5. Known severe renal impairment.

   Severe renal impairment is defined as receiving chronic dialysis or known estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at the time of randomization based on serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see SPM).
6. Any condition, other than vascular disease, with life expectancy <1 year that might prevent the subject from completing the study.
7. Known active tuberculosis, HIV, active opportunistic or life threatening infections.
8. Vaccination with a live attenuated vaccine (see SPM) within 6 weeks of randomization.
9. Concomitant use of cytotoxic chemotherapy for cancer or known ongoing or anticipated use of chronic severe immunosuppressive agents as listed below:
   - Chronic prednisone use >10 mg/day for >14 consecutive days.
   - Currently receiving any systemic immunosuppressive therapy (See SPM for details).
10. Positive pregnancy test or is known to be pregnant or lactating.

    All female subjects of childbearing potential must have a urine or serum β-human chorionic gonadotropin [hCG] pregnancy test performed prior to randomization.
11. Known alcohol or drug abuse within the past 6 months.
12. Any current mental condition (psychiatric disorder, senility or dementia), which may affect study compliance or prevent understanding of the aims, investigational procedures or possible consequences of the study.

13. Use of another investigational product within 30 days or 5 half-lives (whichever is longer) or according to local regulations, or currently participating in a study of an investigational device. Subjects must be randomized only one time in this investigational study.
14. Anticipated inability to comply with any study procedures, including participation in study visits according to the visit schedule through 24 weeks.
15. Any other reason the investigator deems the subject to be unsuitable for the study.

French subjects: In France, a subject will be excluded if he/she has participated in any study using an investigational drug during the previous 30 days.

4.4. Criteria for Early Discontinuation of Investigational Product

The primary analysis of this study will be according to the intent-to-treat (ITT) principle. Every subject, including those who prematurely stop taking IP, are to be followed for the duration of the subject's study period (24 weeks), unless consent for *all* forms of follow-up is actively withdrawn.

The requirements for handling early discontinuations from IP are described below. Details of the requirements for subject follow-up are provided in Section 4.5.

Early Discontinuation of Investigational Product

If a subject permanently discontinues treatment with IP (regardless of the reason) prior to the end of the planned treatment phase, the subject will undergo an IP Early Discontinuation Visit and continue follow-up according to the Time and Events Schedule (Table 1) and Section 4.5.

If the discontinuation occurs at a scheduled visit, the assessments and procedures for the IP Early Discontinuation Visit (Table 1), should be completed instead of that visit.

If a subject discontinues IP (regardless of the reason) between scheduled visits, the subject should be brought into the clinic as soon as possible to complete the IP Early Discontinuation Visit. Subjects with discontinuation of IP prior to 12 weeks should also return for the Week 12 (+2 weeks) visit.

In all cases, reasons for discontinuation of IP and the date of last dose will be recorded.

Possible Reasons for Discontinuation of Investigational Product

Possible reasons for subject discontinuation from IP include, but are not limited to, the following:

- Abnormal liver chemistry(ies) at baseline if certain criteria are met (see Section 6.4.1).
- Adverse experience requiring discontinuation including:
    - Liver chemistry abnormalities exceeding the threshold criteria (as outlined in Section 6.4.1).

- Subject becomes pregnant during the study.
- Need for chronic use of a prohibited concomitant medication
- Clinically significantQT prolongation, not attributed to other reversible factors (Contact TIMI Hotline/Medical Monitor prior to action with IP; see Section 6.4.12)
- Decision by subject or proxy.
- Sponsor terminated study.
- Investigator site closed and subject was unable to transfer to another investigative site.

4.5. Procedures for Subject Follow-up

All subjects who either complete the treatment period or who prematurely discontinue IP are required to undergo clinical assessments to Week 24, according to the Time and Events Table (Table 1).

If a subject prematurely discontinues IP and is unable to attend visits in-person according to the visit schedule, he/she will be contacted by telephone or other methods to assess study outcomes and vital status, unless the subject has actively withdrawn consent for all forms of contact. Follow-up of subjects who withdraw consent for contact is described below.

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of IP.

Other subject follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

Withdrawal of Consent for Contact

Subjects who no longer wish to attend study visits in-person will be asked to be contacted by telephone or other methods to assess study outcomes and vital status. However, if a subject specifically withdraws his/her consent to be contacted for additional information as confirmed by processes detailed in the SPM, no further study visits or study-related telephone contacts can be conducted. Information regarding study outcomes or vital status will be collected if it is available in the public domain. The reason for the subject withdrawing consent for additional contact will be collected. Alternative permitted options to obtain study outcomes and vital status will be summarized on a checklist. For any subject who withdraws consent for contact, the investigator will document/sign the checklist and describe the discussion with the subject regarding each of the contact options that were offered.

Subjects Deemed Lost to Follow-up

Finally, investigators should make every effort to contact subjects who are deemed lost to follow-up, including pursuing any alternative contact methods permitted by local regulations or agreed by the subject. As permitted by local regulations, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Losmapimod (micronized GW856553X) 7.5 mg and matching placebo are supplied by GSK as film-coated, round, plain faced tablets.

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

IP must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of IP will be limited to the investigator and authorized site staff. IP must be dispensed or administered only to subjects randomized in the study and in accordance with the protocol. At hospital discharge IP will be dispensed to subjects; these bottles will be returned to the study site at the Week 12 visit.

All IP, including unopened or partially used containers, must be maintained at the study site for eventual return to GSK or disposal according to local guidelines (refer to the SPM for additional guidance).

Oral doses of losmapimod 7.5 mg, or matching placebo, taken twice daily with or without food and swallowed whole (not chewed), will be added to standard of care in this study. The first dose must be taken prior to PCI, CABG, or administration of fibrinolytic for the qualifying event. Subjects will continue to take one tablet in the morning and one tablet in the evening for 12 weeks. Doses of IP should be separated by at least 6 hours.

If a dose of losmapimod is missed and the time of the next scheduled dose is less than 6 hours, subjects should wait until the next dosing period; however, if the time of the next scheduled dose is greater than 6 hours, the subject should take the missed dose.

Interruption of IP

Investigators may temporarily interrupt IP dosing at their discretion if necessary for the subject's safety; although the duration of the IP interruption should be minimized. If the total duration of IP interruption is more than 2 weeks (or anticipated to be more than 2

weeks), the investigator should contact the medical monitor/TIMI Medical Hotline to review medical reasons and steps undertaken to assure the subject's continued adherence to IP. Permission is not required to resume IP unless there exists a potential safety concern, in which case the GSK medical monitor/TIMI Hotline should be consulted.

In the event that the investigator becomes aware that a subject has interrupted IP, the reason should be identified and medical judgment used to determine the appropriateness of resumption of IP as per above.

The exact dates of investigator-approved and subject-initiated stopping and/or re-starting IP should be recorded in the eCRF. IP should not be re-initiated in subjects who have progressed beyond the 12-week treatment period.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule and randomization must occur before administration of any IP. Separate randomization schedules will be generated for Part A and Part B. The randomization schedules will be center-based and stratified to account for subjects' NSTEMI/STEMI status at baseline. GSK's Registration and Medication Ordering System (RAMOS) will be employed to assign IP to the subjects. The investigator (or designee) must enter a subject into RAMOS once the ICF is signed and the subject is ready to be randomized. One bottle will be dispensed. The bottle allocation is unique to each subject and must not be re-assigned. The first dose of IP should be taken within 2 hours of randomization and before any coronary revascularization or administration of fibrinolytic treatment.

RAMOS is a validated, FDA 21 CFR11 compliant system that allows access to the treatment codes for packaging and supplies purposes. Access to the unblinded treatment codes are password restricted to personnel responsible for packaging IP. All personnel involved with the clinical conduct of the study remain blinded to subject level treatment assignments until all subjects are completed and the final study database is frozen.

5.3. Blinding

Neither the subject nor the study physician will know which of the two treatments (losmapimod or placebo) the subject is receiving. Blinded IP will be provided to the centers as individually coded bottles. The randomization schedule will not be disclosed to the investigator or any personnel involved in the conduct of the study before the database is locked except as described below.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator. Investigators have direct access to the subject's individual study treatment allocation via unblinding options in RAMOS. It is preferred (but not required) that the investigator first contacts the TIMI Medical Hotline (or the GSK Medical Monitor or appropriate GSK study personnel) to discuss options before unblinding the subject's treatment assignment. If the TIMI Hotline (or GSK personnel) is not contacted before the unblinding, the investigator must notify the

TIMI Hotline as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool. If the treatment assignment was unblinded for a subject then the subject should continue taking IP unless the investigator deems it a safety concern for the subject. The subject should remain in the study and continue follow-up according to the Time and Events Schedule (Table 1) and Section 4.5.

Subjects will be provided with a card to be carried at all times during the study to facilitate unblinding in the event of a medical emergency managed by a physician other than the investigator or investigational site staff.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. These reports to investigators will remain blinded with respect to treatment allocation.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of IP dispensed and returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Assessment of subject overall compliance with taking IP (i.e., adherence) will be completed at the Week 12 visit.

At randomization, subjects will be allocated a single bottle of IP containing 200 tablets.This single bottle will be dispensed to the subject by the time of hospital discharge.

At each visit during the treatment phase, investigators and site staff will assess for missed dosing of IP and should reinforce the importance of subjects being compliant with IP dosing requirements

Subjects will be instructed to return any unused IP at the Week 12 visit. All returned IP will be counted to determine the actual number of tablets taken by the subject and recorded in the eCRF. Subjects estimated to have taken less than 80% or more than 120% of IP during the study will be considered as noncompliant. The formula used for calculating compliance is defined in the RAP.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

Investigators will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in ACS will be emphasized during study conduct, including anti-platelet therapy, statin medications, use of appropriate revascularization, ACE inhibitors and beta blockers.

All concomitant medications taken during the study will be recorded in the eCRF. However, concomitant medications taken one time or for one day use such as administered for general anesthesia, or a procedure, or for headache, for example, will not be required to be collected.

5.6.2. Prohibited Medications and Non-Drug Therapies

Except for IP administered for this study, no investigational drugs or new placements of investigational devices are permitted during the study. If a subject develops a need for an exclusionary therapy, the GSK medical monitor/TIMI Hotline should be notified promptly.

Live Attenuated Vaccines

Due to the theoretical risk, live attenuated vaccines should not be administered during the 12-week treatment period with losmapimod, or within the 6 weeks prior to initiation or 4 weeks after stopping IP.

BCRP Substrates with a Narrow Therapeutic Index

There is a low risk of interaction with co-administration of losmapimod with *orally* administered BCRP substrates with a *narrow therapeutic index*. Therefore, in the case of such co-administration, careful monitoring for adverse effects of these agents is advised. A full listing of prohibited medications can be found in the SPM.

5.7. Treatment after the End of the Study

Subjects will be treated as deemed appropriate by the investigator following the end of the Treatment Phase. IP will not be available to subjects after the Treatment Phase (Week 12 visit).

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

5.8. Treatment of Study Treatment Overdose

For this study, any dose of losmapimod >15 mg per day will be considered an overdose. Clinical sequelae of overdosing of losmapimod are not known.

No specific treatment is recommended for an overdose of losmapimod and treatment is at the discretion of the investigator. The GSK medical monitor/TIMI Hotline should be notified promptly.

6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Schedule for the study is shown in Table 1. Afer enrollment of 7,000 subjects in Part A plus Part B1, and subject to approval by the IDMC after review of safety data, the clinic visit at Weeks 4 and 24 (±2 weeks) will be replaced with a focused schedule of assessments via a phone call in Part B2 (Table 1). Participating study sites will be notified if and when the focused schedule of assessments can be adopted for the remainder of the trial. Additional assessments for subjects participating in the renal and expanded laboratory and PK/PD substudies are shown in Table 2 and Table 3, respectively.

Day 1 of the study is the day that the subject is randomized to IP and all study dates should be counted from Day 1.

Table 1 Time and Events Table

	Screening (Prerandomization)	Randomization [a]	Treatment			Follow-up
			Discharge (-2 days)	Week 4 (±2 weeks)	Week 12 (+2 weeks) / IP Early Discontinuation [b]	Week 24 (±2 weeks)
	Hospital			Clinic: Parts A & B1 Phone: Part B2 [c]	Clinic	Clinic: Parts A & B1 Phone: Part B2 [c]
Screening Procedures						
Written informed consent	X					
Subject demography/history	X					
Inclusion/exclusion criteria	X					
Efficacy Assessments (Section 6.3)						
Clinical outcomes		←----------X----------→				
Safety Assessments (Relevant Section)						
Brief physical exam (Section 6.4.13)	X			X [d]	X	
Vital signs (Section 6.4.14)	X			X [d]	X	X [d]
12-lead ECG (Section 6.4.12)[e]		X	X	X [d]	X	
Non-serious AEs (Section 6.4.4) [f]		←---------- X [d] ----------→				
Serious adverse events (Section 6.4.4)	X	←----------X----------→				
AEs of special interest (Section 6.4.6)		←----------X----------→				
AEs leading to permanent discontinuation of IP		←----------X----------→				
Prior/concomitant medication	X		X	X	X	X
Laboratory Assessments (Section 6.4.15)						
Local liver chemistries and creatinine [g]	X (L)					
Clinical chemistry, hematology, and lipids		X (C)		X (C) [d]	X (C) [d]	X (C) [d]

	Screening (Prerandomization)	**Randomization** [a]	**Treatment**			**Follow-up**
			Discharge (-2 days)	**Week 4 (±2 weeks)**	**Week 12 (+2 weeks) / IP Early Discontinuation** [b]	**Week 24 (±2 weeks)**
	Hospital			**Clinic: Parts A & B1 Phone: Part B2** [c]	**Clinic**	**Clinic: Parts A & B1 Phone: Part B2** [c]
HbA1c (diabetics only)		X (C)		X (C) [d]	X (C) [d]	Part A only (C)
HBsAg and hepatitis C antibody		X (C)				
CV biomarkers		X (C)		X (C) [h]	X (C) [h]	Part A only (C)
Genetic sample		X (C)				
Cardiac troponin [i]	X (L)		X (L)			
Pregnancy test [j]	X (L)			X (C/L) + Wk 8	X (C)	
Other Assessments (Section 6.5)						
EQ-5D5L in selected contries			Parts B1 & B2 only		Parts B1 & B2 only	Part B1 only
Study Drug Administration						
Contact RAMOS		X				
IP administration: first dose within 2 hrs of randomization		←----------X----------→				
IP compliance					X	

C, tests done at central laboratory; L, tests done at local laboratory.

If a subject is unable or unwilling to comply with a visit window, then the visit will be conducted as close to the intended visit as possible.

a. Assessments scheduled for randomization to be done prior to administration of the first dose of IP.

b. For subjects who discontinue IP prior to Week 12, the subject should return to the clinic for an Early IP Discontinuation visit. After the Early IP Discontinuation visit, the subject will continue visits according to the study schedule, including returning for a vist at Week 12.

c. Subject to approval by the IDMC after their review of Parts A and B1, the Week 4 and Week 24 visits may be conducted by phone in Part B2. Sites will be notified of the IDMC's approval to moved to the focused plan for assessments. Alternatively, these visits would continue to be in-person clinic visits until IDMC approval is given.

d. Subject to approval by the IDMC after their review of Parts A and B1, the specified assessments will not be performed in Part B2. Sites will be notified of the IDMC's approval to move to the focused plan for safety assessments. Alternatively, these tests will continue until IDMC approval is given.

e. The randomization ECG must be obtained before but no longer than 2 hours prior to the first dose of IP. If baseline QTc>450 msec additional monitoring required during hospitalization (see Section 6.4.12). During the in-hospital period, a 12-lead ECG will be done during screening and for any suspected recurrent ischemic event. Locally obtained ECGs from a subset of subjects (n=1000), at baseline and Week 4 will be overread centrally.

f. Non-serious AEs (not meeting SAE criteria) will be collected from the start of IP until permanent discontinuation of IP. Note that non-serious AEs meeting criteria for AEs of special interest and SAEs have a longer period of reporting (see separate lines for those AEs).

g. If prior results for liver chemistries or creatinine from the local laboratory are available then these may be used to check that the subject qualifies for the study. If local liver chemistries are not available during screening, samples will be collected and sent to the local laboratory for analysis, provided that the subject has signed the consent. It is acceptable to randomize the subject prior to having the results. See Section 6.4.1.
h. Cardiovascular (CV) biomarker sampling may be omitted at Week 4 and Week 12 in part B after the planned review of summary analyses at the end of Part A. See Section 6.6, Appendix 5.
i. Cardiac troponin assessed, whenever possible, at the following time points; pre-dose, prior to PCI or CABG (if >2 hours after pre-dose sample), 6-12 hours post-PCI, 24 hours post-PCI and 48 hours post-PCI or hospital discharge (whichever is first).
j. Urine or serum β-hCG pregnancy test for women of childbearing potential only. Central lab testing (serum β-hCG) will be performed at week 4 (Part A and B1), and week 12. At-home urine pregnancy test required at week 4 (for part B2), and Week 8.

Table 2 Time and Events Table: Additional Assessments for Subjects (n=600) Enrolled in the Renal and Expanded Laboratory Substudy in Part A

		Treatment				Follow-up	
	Pre-randomization/ Baseline (Pre-dose)	In-hospital Period (48±4 hrs post dose)[a]	Week 4 (±2 weeks)	Week 12 (+2 weeks)	Week 13 (±5 days)	Week 18 (±5 days)	Week 24 (±2 weeks)
	Hospital	Hospital	Clinic	Clinic	Clinic	Clinic	Clinic
Clinical chemistry [a]		X			X	X	
NTproBNP	X		X	X			X

a. Obtain the sample within 48±4 hrs after dosing begins or before hospital discharge if earlier than 48 hours.

Table 3 Time and Events Table: Pharmacokinetic Assessments for Subjects (n=3850) Enrolled in the PK Substudy in Part B

	In-hospital Period			Week 4 (±2 weeks)
	Sample 1	Sample 2	Sample 3	Sample 4
PK samples	6-12 hrs post 2nd dose	1-2 hrs post 3rd Dose	3-4 hrs post 3rd Dose	Pre dose sample

6.1. Critical Baseline Assessments

Refer to Table 1 and Table 2 for a list of assessments obtained at Baseline. Medical history and CV medical history/risk factors will be assessed at Baseline. Investigators are encouraged to implement lifestyle modifications and adjust or initiate the appropriate pharmacotherapy throughout the study as recommended by current therapeutic guidelines for subjects randomized in the study.

Some subjects may not have liver chemistry values or calculated eGFR prior to randomization and administration of IP. Therefore, it is acceptable to obtain a blood sample to measure liver chemistry and creatinine to calculate eGFR at the time of randomization and administer IP prior to having the results. Liver chemistry and renal function results from the local laboratory must be available within 24 hours of obtaining the blood sample. See Section 3.1.3 for response to this testing.

6.2. Subject Assessments Related to Potential Ischemic Events and Peri-procedural (PCI/CABG) Myocardial Injury

Potential ischemic events should be assessed for myocardial infarction with serial testing of cardiac biomarkers of necrosis (cardiac troponin preferred) and ECGs. In addition, in order to assess for peri-procedural myocardial injury with coronary revascularization and support CEC adjudication of Type 4a and Type 5 MI, cardiac troponin will be measured locally before and after PCI or CABG whenever performed at the participating study center. Samples for measurement of cardiac troponin will be obtained, whenever possible, at screening, immediately prior to PCI or CABG (if >2 hours after screening sample), 6-12 hours post-PCI, 24 hours post-PCI and 48 hours post-PCI or hospital discharge (whichever is first). In addition, the study investigator (or qualified designee) will review each procedure for specific angiographic or clinical evidence of complications (see SPM for details) and provide procedural records for all events meeting reporting criteria (see SPM) or requested by the CEC.

6.3. Efficacy

An independent CEC will review and adjudicate the following clinical outcomes as potential endpoint events (see endpoints listed in Section 6.3.1 and Section 6.3.3):

- Death will be adjudicated as specifically CV or non-CV. CV death will be further defined as whether it is related to CHD.
- Cardiac ischemic events: MI and unstable angina requiring re-hospitalisation, including SRI-UR. All ischemic events and deaths will also be reviewed for probable or definite stent thrombosis.
- Stroke and transient ischemic attack.
- Hospitalization with suspected HF.

When there is a disagreement between the CEC and the local investigator reported event, the CEC's decision will be considered final. The detailed descriptions of the endpoint definitions necessary for adjudication are contained within the CEC charter. The guiding

principle will be the "Standardized Definitions for End Point Events in Cardiovascular Trials: Draft Definitions for Testing February 4, 2012," and the "Third Universal Definition of Myocardial Infarction" endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) [Thygesen, 2012].

The following endpoints will be captured as recorded by the investigator in the eCRF without adjudication:

- Any coronary revascularization procedure.
- Acute limb ischemia and lower extremity arterial revascularization procedures.
- Any re-hospitalization within 30 days of discharge.

At each visit, information on any potential study outcome will be collected and reported on event specific eCRF pages. Source documentation required to support the adjudication of the events is described in the SPM. Recording of potential endpoint events in the eCRF and submission of source documentation will be required for clinical events meeting reporting criteria (see SPM) whether or not an endpoint event is suspected by the investigator.

6.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the composite measure of adjudicated MACE that includes the time to first occurrence of CV death, MI, or SRI-UR.

If the effect of losmapimod on MACE shows a statistically significant benefit compared to placebo, then the analysis will proceed to testing the hypothesis for the principal secondary endpoint using a serial gate keeping procedure to account for multiplicity.

6.3.2. Secondary Efficacy Endpoints

Principal Secondary Endpoint: The principal secondary endpoint is the time to first occurrence of the composite of adjudicated CV death or MI.

Additional Secondary Endpoints:

- The composite of CV death, MI, or hospitalization for HF.
- The expanded composite of arterial CV events, defined as CV death, MI, SRI-UR, or stroke.
- The composite of coronary events (defined as CHD death, MI, SRI-UR, or any unplanned coronary artery revascularization).

  Planned coronary artery revascularizations are those initial or staged interventions performed based on the initial qualifying ACS.
- The composite of CV death or hospitalization for HF
- The composite of CV death, MI or stroke.

- The composite of CV death, MI, SRI-UR, stroke or hospitalisation for HF
- The primary and principal secondary endpoints will be evaluated replacing CV death separately with CHD death ("Coronary MACE") and all-cause death.
- The primary and principal secondary endpoints will be evaluated replacing all MI with Type 1 (spontaneous) MI.
- Individual components of the composite endpoints (including all-cause mortality).
- Definite or probable stent thrombosis.
- Any re-hospitalization within 30 days of discharge.

For the primary and each of the secondary endpoints, the principal analysis will be through 12 weeks, with additional analyses through 4 and 24 weeks unless otherwise stated. In addition, a recurrent event analysis (i.e., accounting for subjects who experience multiple events) will be conducted for each composite endpoint. Additional endpoints will be specified in the RAP.

All endpoints are defined in detail in the CEC Charter.

6.3.3. Exploratory Endpoints

- Levels of biomarkers of inflammation and CV risk over time
- PK and PK/PD, health status, and genetics.
- Other (non-coronary) atherothrombotic vascular events (acute limb ischemia or lower extremity arterial revascularization for ischemia).

6.4. Safety

6.4.1. Liver Chemistry Stopping and Follow-Up Criteria

Baseline Liver Chemistries and Follow-up

Subjects with known elevation of liver chemistries prior to randomization are excluded from participation in the study (see Section 4.3). However, some subjects may not have liver chemistry values prior to randomization and administration of IP. Therefore, it is acceptable to obtain a blood sample to measure liver chemistry at the time of randomization and administer IP prior to having the results. This sample must be analyzed by the local laboratory and liver chemistry results must be available within 24 hours of obtaining the blood sample.

Actions in the Case of Elevated Baseline Liver Chemistries (Discovered after Randomization)

Refer to Appendix3A.

Liver Chemistry Stopping Criteria

Refer to Appendix3B and Appendix3C.

6.4.2. Monitoring of Subjects with Viral Hepatitis

Hepatitis B: subjects with a positive Baseline HBsAg result.

All randomized subjects will have a baseline blood sample obtained prior to or at the time of randomization that is analyzed by the central laboratory for HBsAg. In subjects with confirmed Hepatitis B surface antigen results, if a subsequent liver chemistry reveals ALT ≥3xULN then hepatitis testing with HBV DNA analysis should be performed immediately (see Appendix 3). A local liver specialist is recommended for consultation to determine if the ALT elevation is likely to have been caused by reactivation or exacerbation of HBV. For subjects diagnosed with HBV, medical care should be according to local standard care.

Hepatitis C: subjects with a positive Baseline Hepatitis C Antibody result.

All randomized subjects will have a baseline blood sample obtained prior to or at the time of randomization that is analyzed by the central laboratory for Hepatitis C antibody. If the result indicates that the subject is positive for Hepatitis C, then the GSK medical monitor/TIMI Medical Hotline should be contacted.

If a blood sample obtained *after* randomization shows ALT ≥3xULN then hepatitis testing with HCV RNA analysis should be performed immediately (see Appendix 3). A local liver specialist is recommended for consultation to determine if the ALT elevation is likely to have been caused by reactivation or exacerbation of HCV. For subjects diagnosed with HCV, medical care should be according to local standard care.

Subjects newly diagnosed with Hepatitis B or C: All subjects newly diagnosed with Hepatitis B or C may remain on IP as long as liver chemistry results do not warrant further action (see Appendix 3). Seeking care from a liver specialist is recommended.

6.4.3. Severe Renal Impairment

Some subjects may not have creatinine levels and calculated eGFR prior to randomization and administration of IP. Therefore, it is acceptable to obtain a blood sample to measure creatinine and calculate eGFR at the time of randomization and administer IP prior to having the results. Renal results must be available within 24 hours of obtaining the blood sample.

If baseline eGFR results indicate severe renal impairment (<30 mL/min/1.73 m^2), then IP may be continued and sites should seek immediate consultation with the GSK medical monitor/TIMI Hotline for appropriate follow-up.

6.4.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.4.4.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure may meet the definition of an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

  Pre-existing disease(s) or condition(s) that lead to an elective hospitalization or procedure in the absence of any worsening of that condition (e.g. elective surgery scheduled only because of convenience during the study period).
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

6.4.4.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death.

b. Is life-threatening.

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization.

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. As noted above, hospitalizations for procedures are not required to be reported as SAEs. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, suicidality intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.4.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.4.6. Adverse Events of Special Interest

Subjects will be monitored for incidences of the following adverse events of special interest (see SPM for details), with data collection on specialized forms, as appropriate:

- Infection:
  - Serious adverse events of infection.
  - Opportunistic infections.
  - Tuberculosis.
- Liver events.
- Bleeding.
- Acute renal failure.

6.4.7. Cardiovascular Events

CV events which are adjudicated as primary or secondary efficacy endpoints (see Section 6.3.2 and Section 6.3.3, respectively) will not be subject to expedited reporting to regulatory agencies regardless of the 'expectedness' or 'relatedness' of the event..

6.4.8. Pregnancy

Any pregnancy that occurs in a subject during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

A female subject who becomes pregnant prior to the end of the Treatment Phase must be immediately withdrawn from IP. Any such subject will continue to be followed for clinical outcomes through the end of the study.

6.4.9. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

SAEs and AEs of special interest will be collected throughout all parts of the study, beginning at the time of first dose of IP through the Week 24 visit. In addition, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy), or **related** to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact at Week 24. All SAEs will be reported to GSK within 24 hours, as indicated in 6.4.11.

Non-serious AEs will be collected from the time of the first dose of IP until the Week 12 Visit, in Part A and Part B1 (Table 1). Non-serious AEs will not be collected in Part B2 if the IDMC recommends a focused safety data collection after reviewing the safety data from subjects in Parts A and B1. However, AEs of special interest (Section 6.4.6) and AEs leading to permanent discontinuation of IP will be continue to be collected in Part B2 (Table 1).

For purpose of clarity, it is reiterated that events that are to be reported as potential study endpoints will be reported in all subjects up to and including the Week 24 Visit. It is expected that investigators will enter potential endpoints events into the subject's eCRF within 24 hours of becoming aware of the event.

6.4.10. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

6.4.11. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

SAEs, non-serious AEs related to study treatment, pregnancies, medical device incidents, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

2. GSK/TIMI Hotline must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

Liver chemistry stopping criteria and follow-up criteria are defined in Appendix 3.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.11.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. These reports to investigators will remain blinded with respect to treatment allocation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.4.12. 12-lead ECG

Full 12-lead ECGs will be recorded at the time points specified in Table 1. All 12-lead ECGs will be read locally by the Investigator or his/her designate. Documentation of the ECG (ECG tracing and investigator interpretation) will be maintained in the subject's source document record.

Those subjects with a baseline QTc interval >450 msec will undergo the following:

- Actively assess and treat potential causes of QT prolongation (e.g. electrolyte disturbance, acute ischemia, and contributing medications) in accordance with clinical care.
- Perform continuous ECG monitoring (i.e. telemetry monitoring) for at least 48 hours while hospitalized with ACS. If the subject is discharged prior to 48 hours of telemetry, a12 lead ECG will be obtained prior to discharge to assess the QTc.
- Obtain a daily 12 lead ECG while hospitalized.
- Obtain pre-discharge ECG 2-4 hours after dosing of IP to evaluate QTc.

Clinically significant QTc prolongation, not attributed to other reversible factors, should be discussed with TIMI hotline/medical monitor.

6.4.13. Physical Examination

Brief physical examination: at minimum, assess weight (enrollment only), height (enrollment only), and perform a focused pulmonary and cardiovascular exam. During hospitalization for the qualifying event, it is acceptable to obtain weight and height at any time prior to hospital discharge.

If possible, the same person should perform the physical exam for an individual subject at each visit for that subject.

6.4.14. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure and resting heart rate. Measurements taken at the hospital prior to randomization will be recorded as the baseline results. Sitting vital signs are taken at each clinic visit prior to obtaining blood samples according to AHA guidelines [Pickering, 2005]. If possible, all measurements should use the same cuff size and same equipment at each visit. (Refer to SPM for more detailed guidelines on taking blood pressure and heart rate measurement).

6.4.15. Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1 and Table 2, must be performed by the central laboratory, unless specified otherwise. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the Central Laboratory. Reference ranges for all safety parameters will be provided to the site by the Central Laboratory.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's eCRF.

All study-required laboratory assessments will be performed by a central laboratory, apart from laboratory tests done at screening to determine subject eligibility (e.g., liver chemistry and renal function tests) (see Section 3.1.3) and to evaluate potential cardiac ischemic events during participation (e.g., cardiac troponin, see Section 6.2). All cardiac biomarker (troponin and/or CKMB) results, where clinically relevant, done by the local laboratory must be entered into the subject's eCRF.

At the Baseline Visit, blood will be collected for HBsAg and hepatitis C antibody and sent to the central laboratory for analysis. If either test is positive, refer to Section 6.4.2.

Blood samples for safety clinical laboratory tests will be collected at the times specified in Table 1 for analysis at the central laboratory, to include:

- *Hematology:* hematocrit, hemoglobin, platelet count, white blood cell count, neutrophil count.
- *Clinical chemistry:* alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, serum albumin, blood urea nitrogen, calcium, chloride, serum creatinine, eGFR,[1] potassium, sodium, bicarbonate, plasma glucose, hs-CRP.
- *Lipids:* total cholesterol, high density lipoprotein cholesterol (HDLc), LDLc, triglycerides.
- *Other:* in subjects with type 1 or 2 diabetes mellitus - HbA1c.

  For lipids, plasma glucose, and HbA1c: The subjects should fast whenever possible for ≥8 hours prior to obtaining the blood sample. For pre-randomization blood samples, obtain the sample even if the subject has not fasted for at least 8 hours.
- *CV Biomarkers*: discussed in detail in Section 6.6, Appendix 5 .

In addition, in the Renal and Expanded Laboratory Substudy (Part A), blood samples will be obtained in a subset of subjects to assess clinical chemistry, as well as other cardiovascular biomarkers, more frequently (Table 2). The target enrollment for this substudy is 600 subjects who complete at least the in-hospital period of laboratories. Enrollment in the substudy will be monitored such that approximately equal proportions of STEMI, and NSTEMI will be recruited.

For females of child-bearing potential, pregnancy testing will be performed at the time points specified in Table 1. A urine β-hCG pregnancy test will be done or serum β-hCG will be assessed according to Table 1. At the time points when a clinic visit is not scheduled, the subject should perform the pregnancy test using an at-home urine pregnancy test kit. The results of the at home pregnancy test at Week 8 can be captured at the next in clinic visit. Any positive test at home should be reported immediately to the site. A positive urine pregnancy test may be confirmed by sending a serum sample to the central laboratory for analysis of β-hCG.

6.5. Health Outcomes: EQ-5D

The EuroQOL five dimension questionnaire (EQ-5D; EuroQol Group) is a standardized instrument for use as a measure of health outcome that provides a simple descriptive profile and a single index value for health status. The EQ-5D self-report questionnaire consists of two parts comprising the EQ-5D descriptive system and the EQ visual analogue scale (VAS). Complete instructions for completion are provided in the SPM.

The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension comprises five levels (no problems, slight problems, moderate problems, severe problems, and extreme

[1] Based on serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

problems) and is referred to as the EQ-5D-5L. A unique EQ-5D-5L health state index value is defined by combining one level from each of the five dimensions.

The EQ VAS records the respondent's self-rated health status on a vertical graduated visual analogue scale (0=worst imaginable – 100=best imaginable). This questionnaire is to be administered in select countries based on local Health Technology Assessment requirements, and will supplement cost effectiveness analyses.

Health status will be assessed for subjects participating in a select number of countries in Part B1 and B2 at the times specified in Table 1 (Part B1: at discharge, Week 12, and Week 24, end of study; Part B2: at discharge and Week 12 only). The paper questionnaire will be completed by the subject at the designated clinic visits and it will not be completed at the Week 24 phone visit in Part B2.

For analysis purposes, EQ-5D-5L data will be pooled from Part B1 and B2 for the discharge and Week 12 visits. A separate subanalysis will be performed for those subjects in Part B1 for whom three data points are available, to assess if the health status data persists at Week 24.

6.6. Biomarkers

Blood samples to assess biomarkers of CV disease and response will be taken in all subjects enrolled in the study, at the times specified in Table 1. Biomarker samples will be stored by GSK and/or TIMI or one of their appointed designees. Additional description of the CV biomarkers is in Appendix 5 and the assessments are considered exploratory.

Blood samples to assess hsCRP will be obtained from all subjects in Part A at designated time points (Table 1). In addition, in an expanded laboratory substudy in Part A, blood samples will be obtained in a subset of 600 subjects to assess NTproBNP and hsCRP (Table 2, Appendix 5). Enrollment in the substudy will be monitored such that approximately equal proportions of subjects with STEMI, and NSTEMI will be recruited.

6.7. Genetic Research

Information regarding genetic research is included in Appendix 4

6.8. Pharmacokinetics

Blood samples for PK analysis of losmapimod will be collected at the time points indicated in Table 3 and as detailed below from approximately 3850 subjects (~1925 subjects on active treatment) in Part B. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Deviations from the defined PK sampling scheme will not be considered protocol deviations.

- *In-hospital period:* During the in-hospital period PK samples should be drawn following the second and third dose. Following the second dose, samples should be collected within the following windows: 6–12 hours post dose (trough sample).

Following the third dose, samples should be collect within the following windows: 1–2 hours post-dose and 3–4 hours post dose. The exact time the PK samples are drawn and the exact time all doses are administered during the in-hospital period should be recorded in the source documents and entered into the CRF.

- *Week 4:* A blood sample should be drawn just prior to dosing of IP on the day of the Week 4 visit. The exact dosing times of IP on the day of each visit and on the day prior to each visit should be recorded in the source documents and entered into the CRF. For the doses prior to the visit, subjects should return a card on which the subject records this dosing information.

Details of the PK blood sample collection (included volume to be collected), processing, storage, and shipping procedures are provided in the laboratory manual.

7. DATA MANAGEMENT

For this study, subject data will be entered into a GSK-defined eCRF, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

This study is an operationally seamless design to be conducted in two stages (Part A and Part B) as described in Section 3.1. The primary inference for efficacy will be based on an assessment of the data from the main event driven cohort (Part B).

The primary inference for safety will be based on an assessment of the combined safety database from both cohorts (Part A + Part B).

In summary, the primary analysis of MACE at 12 weeks will be based on a stratified log-rank test with a stratified Cox-regression model used to estimate the hazard-ratio and its 95% confidence interval (both analyses stratified by NSTEMI/STEMI). Key secondary endpoints will be assessed using the same methods as the primary endpoint, with overall significance controlled for multiplicity at the 5% level. With 1,400 primary events the study would have 90% power for statistical significance at $p < 0.05$ based on a true benefit of 16% relative risk reduction. Further details are described below.

8.1. Hypotheses

The primary efficacy analysis (Part B) will assess the time to first occurrence (in days) of MACE from randomization up to and including Week 12 (Day 84).

The primary objective of the study is to assess superiority of treatment with losmapimod relative to placebo on top of a background of standard care.

The primary analysis will assess superiority of treatment with losmapimod relative to placebo on time to first occurrence of MACE through 12 weeks of therapy. Statistical significance will be asses at the two-sided 5% level by a log-rank test, stratified by NSTEMI/STEMI status at baseline.

A two-sided 5% significance level will be used to test the following hypotheses:

- Null hypothesis: The hazard functions for MACE are the same for both losmapimod and placebo treated subjects
- Alternative hypothesis: The hazard functions differ between losmapimod and placebo treated subjects

A stratified Cox-regression model, stratified by NSTEMI/STEMI, will be used to estimate the hazard-ratio and its 95% confidence interval. A hazard ratio < 1 will correspond to a benefit of losmapimod relative to placebo.

The primary efficacy endpoint (MACE) will be tested first and if the null hypothesis is rejected, the principal secondary endpoint (CV death or MI) will be tested, before proceeding to other secondary endpoints as part of a serial gate keeping procedure, the details of which are are addressed in the RAP. If either the primary or principal secondary null hypotheses fail to be rejected, the other secondary endpoints will be tested in an exploratory manner.

8.2. Study Design Considerations

The study is designed to assess superiority of treatment with losmapimod relative to placebo on top of a background of standard care. It will be a randomized, placebo-controlled, double-blind, parallel group, international, multicenter, two-stage design.

In total, approximately 25,500 ACS subjects will be recruited, comprising 3,500 subjects in a leading cohort (Part A) used to provide an initial assessment of safety and exploratory efficacy with approximately 200 MACE (defined as CV death, MI, or severe recurrent ischemia requiring urgent coronary artery revascularization); followed by a main cohort of approximately 22,000 subjects (event target of 1,400 MACE and 1,000–1,200 CV death or MI).

8.2.1. Sample Size Assumptions

Assessment of MACE Efficacy from Part A

The pivotal and powered assessment of efficacy will be provided by Part B of the study, with Part A providing an exploratory assessment to support continuation to Part B.

Whilst an exploratory cohort could not be well powered for formal assessment of efficacy, the precision with which the MACE effect size can be estimated from Part A has been considered. For example, with approximately 200 subjects anticipated to experience at least one MACE event, an observed relative risk of 0.8 would have an associated 95% confidence interval of approximately 0.61 to 1.05, whilst an observed relative risk of 1.0 would have a 95% confidence interval of approximately 0.76 to 1.31. Given the limitations on precision that would be expected in an exploratory context, the decision to progress to Part B will be multifaceted.

Assessment of Efficacy in Part B

The size of Part B has been determined based on an event target of 1,400 adjudicated primary endpoint events. It is anticipated that approximately 22,000 subjects will be

recruited to achieve this event target. The primary endpoint event target is expected to include 1,000–1,200 CV death or MI events. These estimates are based on a projected 12 week MACE event rate of ~7% for the placebo group, and an assumed 20% relative risk reduction for subjects in the losmapimod group. Within the composite of MACE, it is estimated that the incidence of CV death/MI will be 5% to 6% and that SRI-UR will be 1% to 2%.

The principal efficacy evaluation will occur up to Week 12 with additional evaluations of efficacy at Weeks 4 and Week 24.

A total of 1,400 adjudicated primary MACE events (CV death, MI, and SRI-UR) occurring within the principal study time point of 12 weeks will provide approximately 90% power to detect a 16% reduction in risk (hazard ratio=0.84) at a 5% significance level. At the 5% significance level, the minimum detectable effect (i.e., the smallest effect to give a significant p-value) is approximately 10%.

The principal secondary endpoint of CV death/MI will be tested provided the primary endpoint is statistically significant at the 5% level. For the principal secondary endpoint of CV Death or MI: a minimum of 1,000 adjudicated events will provide approximately 90% power to detect an 18.5% reduction in risk (hazard ratio=0.815) and close to 80% power to detect a 15% reduction in risk at a 5% significance level. At the 5% significance level, the minimum detectable effect (i.e., the smallest effect to give a significant p-value) is approximately 12%.

The anticipated placebo MACE event rate (~7%) is estimated from the ticagrelor treatment group of the PLATO study using the individual Kaplan-Meier cumulative event rate estimate from the NSTEMI (7.1%) and STEMI (6.0%), taking into account a 20% reduction in events as a consequence of the recent changes to the universal definition of MI and the use of SRI-UR as a replacement for stroke.

The aggregate event-rate data will be periodically reviewed by the Executive Committee and sponsor. Should emerging data diverge significantly from protocol assumptions the total sample size to achieve the event target for Part B may be adjusted if deemed appropriate.

Recruitment may be closed prior to 1400 events if the sample size for part B is anticipated to exceed 24,000 subjects.

Assessment of Safety in Parts A & B1

All 25,500 subjects estimated to enroll in the trial would contribute to a robust overall safety database of clinical adverse events, including liver events.

In addition, the totality of available safety data from Part A (N=3,500) will be evaluated prior to starting Part B, and an additional formal evaluation of safety will be conducted by the IDMC once Part B has enrolled approximately 3,500 subjects (completion of Part B1), to support a combined analysis of 7,000 subjects' safety data. After this point, if considered appropriate by the IDMC, the time and events schedule for data collection will be revised (Section 6). As noted, such decisions will be made based on the totality of

the data, but for illustrative purposes, power and detectable effect with respect to aspects of safety analysis has been considered.

Based on an anticipated placebo incidence of ALT ≥3xULN of 2.5%, if there is a true underlying absolute risk increase with losmapimod of 1.2% (approximate relative increase of 1.5-fold), then with 7,000 patients at the end of Part B1 there is 83% power to observe a significant difference. The smallest observed risk difference that would reach statistical significance (i.e., the minimal detectable effect) is ~0.8% (approximately 30% increase in relative-risk increase terms) at a 2-sided 5% level.

8.2.2. Sample Size Sensitivity

If the placebo event rate for MACE at 12 weeks in Part B is lower than the assumed 7%, the resulting impact on the number of MACE events / the number of subjects to achieve 1,400 MACE events in the main cohort is shown in Table 4 assuming a 20% treatment effect (HR=0.8).

Table 4 MACE Sensitivity for Varying Placebo Event Rates

Placebo Event Rate (at 3 months)	Number of Subjects to achieve 1,400 MACE†	Number of MACE (from 22,000 subjects)†
7.1%	21,900	1,400
7.0%	22,100	1,380
6.8%	22,800	1,340
6.6%	23,500	1,300
6.4%	24,200	1,270
6.2%	25,000	1,230
6.0%	25,900	1,190

† Subject numbers are rounded to the nearest 100. Event numbers are rounded to the nearest 10 events.

8.2.3. Sample Size Re-estimation

The aggregate event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design. Should emerging data diverge significantly from protocol assumptions, the total sample size will be adjusted, within the bounds of feasibility, to achieve the event target for Part B.

8.2.4. Decision-making Criteria for Part A

The assessment of safety and efficacy in subjects with ACS is multi-faceted and hence there is no single decision algorithm for initiating Part B under all possible scenarios. However, a decision to proceed to Part B can only be made with endorsement with respect to safety from the IDMC. With respect to efficacy, a risk reduction in the incidence of the primary endpoint (the composite of adjudicated MACE), accompanied by supporting secondary endpoint data, may be considered an indication to begin enrollment in Part B, provided the IDMC has not identified any meaningful safety concerns.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The primary population for all analyses of MACE, secondary time-to-event outcomes and other efficacy assessments will be the All Randomized (ITT) Population. Subjects will be analysed according to the treatment to which they were randomized.

The primary population for safety in the study will be based on all randomized subjects from Part A and Part B combined, who have received at least one dose of IP. Subjects will be analysed according to the treatment which they actually received.

Any further populations to be used for the assessment of PK, biomarker, genetic and health economic outcomes data will be defined in the RAP.

8.3.2. Analysis Data Sets

The primary inference for efficacy in the study will be made from the analysis of subjects randomized in Part B of the trial. The primary efficacy dataset will comprise all adjudicated events occurring post randomization up to and including Week 12 [Day 84] (including events collected after discontinuation of IP).

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparison of interest is the comparison of the survival functions of adjudicated MACE followed by CV death or MI in a closed testing procedure for losmapimod vs. placebo (using a stratified log-rank test) in Part B. The ITT population will be utilized for this comparison. The comparison will be performed for events occurring within the period from randomization to Week 12 at the two-sided 5% significance level.

8.3.3.2. Other Comparisons of Interest

Leading Cohort (Part A)

The primary efficacy comparison for the leading cohort will be the comparison of the incidence and hazard rates of adjudicated and pending MACE events for losmapimod vs. placebo occurring to Week 12 during Part A of the study.

Secondary Endpoints

The relative effects of losmapimod vs. placebo will also be compared across a number of secondary endpoints.

Secondary efficacy outcomes are defined in Section 6.3.2

The primary and each of the secondary endpoints will be analysed through 4, 12, and 24 weeks unless otherwise stated.

Due to the reduced number of events for the secondary outcomes the analyses may have less power in which case they would be less likely to achieve statistical significance. Details of additional multiplicity considerations are provided in the RAP.

Combined Analysis of Parts A and B

A supportive analysis of efficacy will be performed for the primary and secondary endpoints combining data from Part A and Part B. Further details are provided in Section 8.3.5.1.

8.3.4. Interim Analysis

An IDMC will review data from both stages periodically throughout the trial and may recommend stopping the trial for safety at any time.

There are no plans to stop either part of the study early for benefit and in particular this will expressly not occur during review of Part A. Should, in the course of reviewing mortality data for safety, the IDMC consider a recommendation to stop Part B early for a highly significant difference in mortality (e.g., $p<0.001$) favoring losmapimod (i.e., efficacy) then both the primary endpoint and the principal secondary endpoint would be examined at that time and compelling evidence of benefit for both the primary endpoint and the principal secondary endpoint would be required e.g., $p<0.001$ (using a Haybittle-Peto like approach). This approach would essentially preserve the alpha level at 5% in the final analysis and therefore there are no plans to adjust the alpha level in the final analysis. The timing and number of planned evaluations of safety, as well as assessments for futility, by the IDMC will be specified in the separate IDMC Charter.

The analysis of Part A is not considered to be an interim analysis as the primary inference for the study will be determined only from the subjects in Part B of the trial.

8.3.5. Key Elements of Analysis Plan

Any deviations from the original analysis planned in the protocol agreed upon prior to finalization of the RAP, will be described in that document. Any additional changes to the planned analysis will be described in the final clinical study report.

8.3.5.1. Efficacy Analyses

The primary analysis will be based on a stratified log-rank test with a stratified Cox-regression model used to estimate the hazard-ratio and its 95% confidence interval (both analyses stratified by NSTEMI/STEMI). Key secondary endpoints will be assessed using the same methods as the primary endpoint, with overall significance controlled for multiplicity at the 5% level.Cumulative event rates will be calculated using the Kaplan-Meier method through to 12 weeks.

Treatment comparisons will be presented as forest plots of the hazard ratios and 95% confidence intervals and the effect over time illustrated with Kaplan-Meier plots. Analyses that combine data from Parts A and B will further stratify on which part of the

study subjects were enrolled, in addition to NSTEMI/STEMI status. The validity of the proportional hazards assumption will be assessed (details will be provided in the RAP).

Center-based randomization is planned for operational efficiency in managing drug supply, with a centrally administered randomization code consisting of permuted blocks stratified according to centre. However, as the use of center is purely for operational purposes it is not planned to include centre as a stratification parameter in the statistical analyses.

Sensitivity Analyses

Sensitivity analyses of the primary efficacy endpoint will be performed to assess the robustness of the primary inferences made from the main cohort (Part B).

- An analysis of on-treatment adjudicated MACE (including up to 3 days post discontinuation of IP ≈ 5 half-lives) will be performed in the ITT population.

Analyses of efficacy will be performed for pre-specified subgroups to support the proposed indication. Subgroups and covariates of specific clinical interest include (but are not limited to) type of ACS event (NSTEMI or STEMI), intent for early invasive vs. conservative management, gender, diabetes status, age, time from symptom onset to treatment, and baseline hsCRP levels. Further details will be defined in the RAP.

Multiplicity

Issues related to multiplicity arising from testing the primary endpoint and the principal secondary endpoint and other key endpoints (defined in Section 6.3.2) will be addressed using a serial gate keeping procedure. Further details relating to multiplicity will be addressed in the RAP.

8.3.5.2. Safety Analyses

The total AE experience (non-serious combined with serious AEs) will be reported based on the on-treatment period in accordance with the time-and-events schedule (Table 1). SAEs and AEs of special interest occurring after discontinuation of IP will also be reported. Full details of all safety data reporting (including laboratory data) will be described in the Analysis Plan.

The primary population for all safety assessments will be the Safety Population, defined as all randomized subjects who have received at least one dose of IP. Subjects will be analysed according to the treatment which they actually received. Clinical interpretation will be based upon review and displays of AEs, laboratory values and vital signs. All AE data will be coded using MedDRA and all medication terms will be coded using GSKDrug. Additionally, safety data will be summarized for the leading cohort (Part A) prior to the initiation of the main phase of the study (Part B).

Additional details regarding planned statistical analyses for safety data will be provided in the RAP.

8.3.5.3. Health Outcomes Analyses

Health economic outcomes will be assessed in this study including medical resource utilization and health status asssessment, which will both be used to assess the cost-effectiveness of losmapimod in the ACS population. With the exception of EQ-5D-5L, the events of interest will be measured at discharge, Week 4, Week 12, and Week 24 (end of study) with possibility for an extension registry. The EQ-5D-5L will be collected in a select number of countries in Part B1 at discharge, Week 12, and Week 24 (end of study), while it will be collected in those same countries in Part B2 at discharge and Week 12 only. The paper questionnaire will be completed by the subject at the designated clinic visits and it will not be completed at the Week 24 phone visit in Part B2.

The health economic evaluations, to be detailed in a separate Economic Statistical Analysis Plan, will include: total treatment costs; cost per vascular event avoided; cost per life years saved (LYS); and cost per quality-adjusted life years (QALY) gained.

8.3.5.4. Biomarker Analyses

Details regarding planned statistical analyses for biomarker data will be provided in a separate RAP.

8.3.5.5. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

The objective of the pharmacokinetic analyses is to further develop the population PK model previously developed in Phase 2 in order to predict individual losmapimod exposures. The population PK model will be parameterized for oral clearance (CL/F), apparent volumes of distribution of the central compartment (V2/F) and other parameters specific to the model. The potential effects of subject demographics (e.g., age, sex, weight, concomitant medications, and concurrent diseases) will be examined for their effect on clearance and volume.

The plasma concentration data will be analyzed with the use of the nonlinear mixed effects modeling program NONMEM (version 7.2 or higher). The prior PK model developed from data collected in the SOLSTICE trial will be used as prior information for this analysis. The inital estimation method to be used will be the iterative two-stage (METHOD=ITS) followed by METHOD=BAYES. The objective function will be obtained by importance sampling using the EONLY=1 option.

During each step in the model building process, improvements to the model will be assessed by evaluation of the agreement between the observed and predicted plasma concentrations, reductions in the range of weighted residuals, uniformity of the distribution of the conditional weighted residuals versus the predicted concentrations about the line of identity, and increases in the precision of the parameter estimates, as well as reduction of the terms for inter-individual variability and random residual variability. Assessment of the log likelihood ratio test will also be conducted as a means of assessing improvement in the model.

Once a final pharmacokinetic model has been developed, individual steady-state AUC(0-τ) values will be generated from the individual Bayes estimates of clearance. These

exposure values will be used along with adverse event data in a logistic regression analysis in order to determine if a relationship exists between losmapimod exposure and adverse events.

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GlaxoSmithKline. All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Details regarding the planned statistical analyses of the PK/PD data will be provided in a separate Data Analysis Plan (DAP)

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent, as governed by local regulations, must be obtained from each subject prior to participation in the study. It is anticipated that some subjects will have some or all of the study qualification procedures done as part of routine care outside of the auspices of this study. The data from these procedures may be used to assess eligibility and recorded in the eCRF as long as the subject has signed the informed consent.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., genetic assessments

described in Appendix 4, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

The study will complete when the last subject randomized completes the 12-week treatment period and the 12-week observational follow-up (Week 24 visit).

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The signatory investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have

the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide all of the study investigators with the full summary of the study results within one year of completion of the study. The investigators are encouraged to share the summary results with the study subjects, as appropriate.

Upon request, GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV). For this study, the timing of such posting of a results summary would be after completion of Part B, or after Part A if a decision is made not to proceed with Part B. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature. For this study, the timing of such publication would be at the time the results of Part B are published as a manuscript in the scientific literature, or Part A if a decision is made not to proceed with Part B.

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

10. REFERENCES

Anderson J.L. Adams C.D. et al 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol. 2013;61(23):e179-e347.*

Buffon A, Biasucci LM, Liuzzo G, et al. Widespread coronary inflammation in unstable angina. *N Engl J Med*. 2002;347:5–12.

Buja LM, Willerson JT. Role of inflammation in coronary plaque disruption. *Circulation*. 1994; 89:503-505.

Cheriyan J, Webb AJ, Sarov-Blat L, et al. Inhibition of p38 mitogen-activated protein kinase improves nitric oxide-mediated vasodilatation and reduces inflammation in hypercholesterolemia. *Circulation*. 2011;123:515-24.

Ding C. Drug evaluation: VX-702, a MAP kinase inhibitor for rheumatoid arthritis and acute coronary syndrome. *Curr Opin Investig Drugs*. 2006;7:1020-5.

Elkhawad M, Rudd JH, Sarov-Blat L, et al. Effects of p38 Mitogen-Activated Protein Kinase Inhibition on Vascular and Systemic Inflammation in Patients With Atherosclerosis. *JACC Cardiovasc Imaging*. 2012;5:911-22.

Glaser R, Selzer F, Faxon DP et al. Clinical Progression of Incidental, Asymptomatic Lesions Discovered During Culprit. *Circulation*. 2005;111:143-149.

GlaxoSmithKline Document Number WM2004/00033/09. Study ID GW856553X. GW856553 Investigator's Brochure. Report Date 02-Apr-2013

Goldstein JA, Demetriou D, Grines CL et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *New Engl J Med*. 2000; 343: 915-22.

Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999-3054.

Hommes DW, Peppelenbosch MP, van Deventer SJ. Mitogen activated protein (MAP) kinase signal transduction pathways and novel anti-inflammatory targets. *Gut*. 2003;52:144-51.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos*. 2009; 37: 1779-1784.

Ju H, Behm DJ, Nerurkar S, Eybye ME, et al. p38 MAPK inhibitors ameliorate target organ damage in hypertension: Part 1. p38 MAPK-dependent endothelial dysfunction and hypertension. *J Pharmacol Exp Ther*. 2003;307:932-8.

Li Z, Ma JY, Kerr I, et al. Selective inhibition of p38alpha MAPK improves cardiac function and reduces myocardial apoptosis in rat model of myocardial injury. *Am J Physiol Heart Circ Physiol*. 2006;291:H1972-H1977.

Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868-874.

Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics-2010 update: a report from the American Heart Association. *Circulation*. 2010, 121:e46–e215.

Marber MS, Rose B, Wang Y. The p38 mitogen-activated protein kinase pathway - a potential target for intervention in infarction, hypertrophy, and heart failure. *J Mol Cell Cardiol*. 2011;51:485–490.

Maseri A and Fuster V. Is there a vulnerable plaque? *Circulation*. 2003;107:2068.

Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. *J Am Coll Cardiol*. 1998;31:1460-5.

Moylan C, Suzuki A, Papay JI, et al. A premarketing ALT signal predicts post-marketing liver safety. *Regul Toxicol Pharmacol.* 2012; 63: 433-439.

O'Connor RE, Brady W, Brooks SC, et al. Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S787-S817.

O'Gara P.T. , Kushner F.G. et al , 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol. 2013; 61(4):e78-e140.*

Pickering TG, Hall J, Appel L, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurements in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*. 2005;45:142-61.

Sarov-Blat L, Morgan JM, Fernandez P, James R, Fang Z, Hurle MR, Baidoo C, Willette RN, Lepore JJ, Jensen SE, Sprecher DL. Inhibition of p38 mitogen-activated protein kinase reduces inflammation after coronary vascular injury in humans. *Arterioscler Thromb Vasc Biol*. 2010;30:2256-63.

Schett G, Zwerina J, Firestein G. The p38 mitogen-activated protein kinase (MAPK) pathway in rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:909-916.

Scirica BM, Morrow DA, Cannon CP, et al. Clinical application of C-reactive protein across the spectrum of acute coronary syndromes. *Clin Chem*. 2007; 53: 1800–7.

Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011;58:2432-46.

Standardized Definitions for End Point Events in Cardiovascular Trials: Draft Definitions for Testing February 4, 2012.

Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di MC, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J*. 2012. 33:2569-619.

Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551-67.

Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndrome. *New Engl J Med*. 2009; 361:1045-1057.

Wiviott SD, de Lemos JA, Cannon CP et al. A tale of two trials. A comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE-IT-TIMI-22. *Circulation.* 2006;113:1406-14.

Xu L, Chen S and Bergan RC. MAPKAPK2 and HSP27 are downstream effectors of p38MAP kinase-mediated matrix metalloproteinase type 2 activation and cell invasion in human prostate cancer. *Oncogene*. 2006;25:2987-2998.

Yusuf S, Mehta SR, Zhao F, Gersh BJ, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation*. 2003;107:966-72.

11. APPENDICES

11.1. Appendix 1: Highly Effective Methods For Avoiding Pregnancy In Females Of Childbearing Potential

The following is the all inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

- Abstinence from penile-vaginal intercourse, when this is the preferred and usual lifestyle [Hatcher, 2007a].
- Oral contraceptive, either combined or progestogen alone [Hatcher, 2007a]
- Injectable progestogen [Hatcher, 2007a].
- Implants of etonogestrel or levonorgestrel [Hatcher, 2007a].
- Estrogenic vaginal ring [Hatcher, 2007a].
- Percutaneous contraceptive patches [Hatcher, 2007a].
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the SOP effectiveness criteria as stated in the product label [Hatcher, 2007a].
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject [Hatcher, 2007a]. The information on the male sterility can come from the site personnel's: review of subject's medical records; medical examination of the subject and/or semen analysis; or interview with the subject on his medical history.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicidea (foam, gel, film, cream, or suppository) [Hatcher, 2007b]
- Nonoxynol-9 is the critical component in most spermicides, and is regarded as an acceptale spermicidal agent. Concern has been raised that nonoxynol-9 damages the epithelial lining of the vagina, and exposure may facilitate transmission of viruses, particularly human immunodeficiency virus (HIV). The World Health Organization (WHO) conducted a technical consultation in October 2001 and concluded that the increased risk for such transmission was low to minimal [World Health Organization. WHO/CONRAD, 2003].

References

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007 (a):24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007 (b):28.

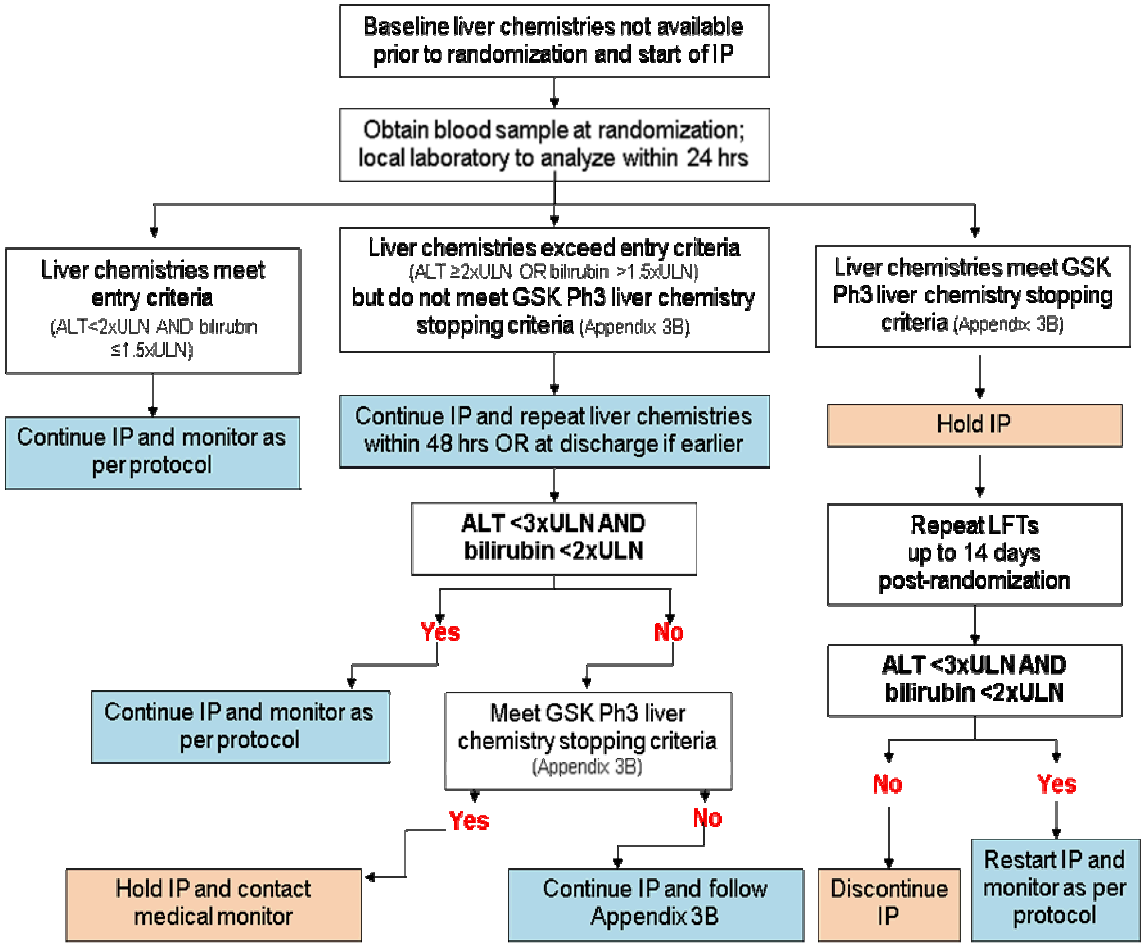
World Health Organization. WHO/CONRAD. Technical consultation on nonoxynol-9. World Health Organization; Department of Reproductive Health and Research; Geneva; 9-10 October 2001. Summary Report. 2001. WHO/RHR/03.8.

11.2. Appendix 2: Country Specific Requirements

No country-specific requirements exist.

11.3. Appendix 3: Liver Chemistry Stopping and Follow-up Criteria

Appendix3A: Baseline Liver Chemistries and Follow-up



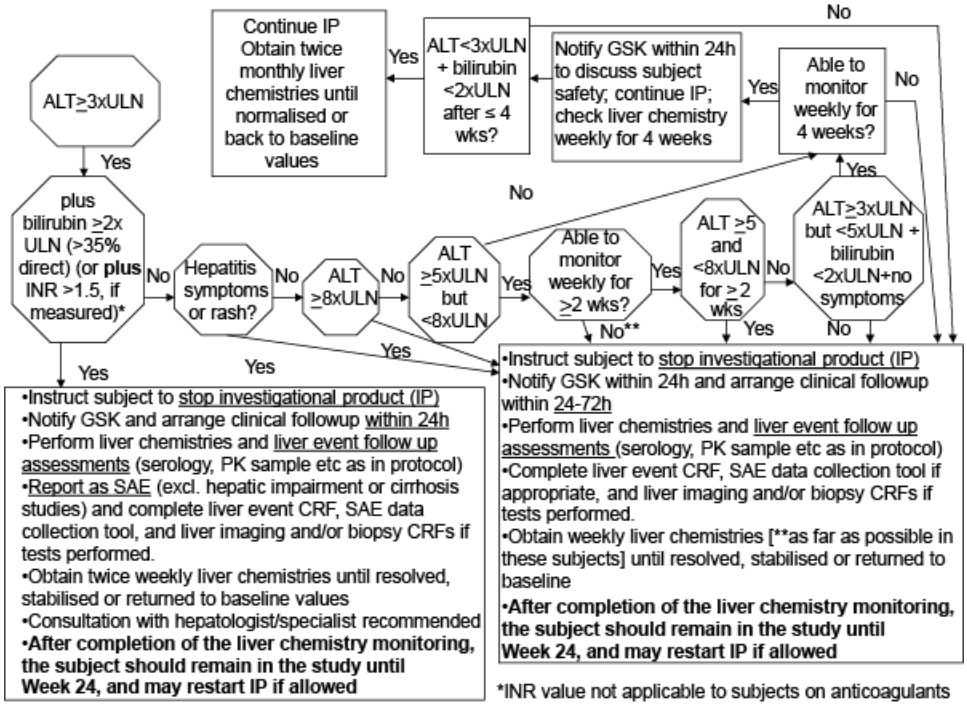
Actions in the Case of Elevated Baseline Liver Chemistries (Discovered after Randomization)

Refer to flow diagram above.

1. If Baseline ALT or bilirubin meets the liver chemistry stopping criteria, hold IP. Refer to flow diagram above for appropriate followup of the subject.
2. If Baseline ALT is ≥2xULN or bilirubin is >1.5xULN but do not meet the liver chemistry stopping criteria, continue IP and obtain a repeat sample within 48 hours or at hospital discharge if earlier.
    - If the repeat ALT is <3xULN, and bilirubin is <2xULN continue IP. Subsequent testing according to usual study schedule (Table 1).

- If the repeat ALT is ≥3xULN or bilirubin is ≥2xULN but do not meet liver chemistry stopping criteria, continue IP and monitor ALT and bilirubin as needed in accordance with Appendix3B (below).
- If the repeat ALT and bilirubin results meet any of the liver chemistry stopping criteria , hold IP. Refer to flow diagram above for appropriate followup of the subject.

Appendix3B: Phase III-IV Liver Safety Algorithms



Note: This algorithm does not apply to liver chemistry abnormalities prior to any administration of investigational product, (where the results are not available pre-randomization). Refer to algorithm (Appendix3A) for appropriate follow-up of those subjects.

Liver Chemistry Stopping Criteria

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria 1-7 are defined below and are presented graphically in the figure above:

1. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and INR>1.5, if INR measured, (in any subject who is not receiving anti-coagulant therapy).

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥3xULN and bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥8xULN.
3. ALT ≥5xULN but <8xULN persists for ≥2 weeks
4. ALT ≥3xULN but <5xULN persists for ≥4 weeks
5. ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
6. ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
7. ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks

When any of the liver chemistry stopping criteria 1-7 is met, refer to Appendix3C "Followup for Liver Chemistry Stopping Criteria 1-7".

Appendix3C: Followup for Liver Chemistry Stopping Criteria 1-7

- **Immediately** withdraw investigational product for that subject
- Report the event to TIMI Medical Hotline/GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% director ALT ≥3xULN and INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE.** Note that baseline liver chemistries not available prior to randomization and start of IP and subsequently found to have ALT ≥3xULN **and** bilirubin ≥2xULN will not be reported as an SAE or considered to have met Hy's Law criteria.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- After completion of the liver chemistry monitoring, the subject should remain in the study until Week 24.

For subjects whose baseline liver chemistries not available at the time of randomisation are subsequently found to exceed GSK's Phase 3-4 liver chemistry stopping criteria, IP will be held. As per Appendix3A, if repeat liver chemistries up to 14 days in these subjects fall to within a defined criteria, IP can be restarted. For all other new abnormalities of liver chemistries that meet IP stopping criteria after randomization, do not restart IP. In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.
- A specialist hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24–72 hrs** for repeat liver chemistries and liver event follow up assessments (see below).
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the TIMI Medical Hotline/GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.

  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.
- Blood sample for PK analysis should be obtained within 72 hours of the last dose of IP. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Total IgG
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China.**
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

11.4. Appendix 4: Genetic Research

Background

There is increasing evidence that an individual's genetic background (i.e., genotype) may impact their risk of clinical outcomes and/or their response to pharmacotherapy including pharmacokinetics (PK) (ie, absorption, distribution, metabolism, elimination), pharmacodynamics (PD) (ie, relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability).

Genetic Research Objectives

The objective of the exploratory genetics research is to investigate the association between genetics variants and the handling or response to losmapimod or any treatment regimen or concomitant medications used in the study and susceptibility to cardiovascular disease and its risk factors/or associated diseases or conditions . Specifically, we may investigate the relationship between genetic variants or genetically defined disease subtypes and each of the following:

- Relationship between genetic variants and the PK and/or PD of losmapimod or relevant drugs
- Relationship between genetic variants and safety and/or tolerability of losmapimod or relevant drugs
- Relationship between genetic variants or genetically defined disease subtypes to clinical efficacy of losmapimod and clinical study outcomes.
- Natural history of heart and vascular disease, and disease-based outcomes.

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives study medication may take part in the genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Subject participation in the genetics research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

In addition to any blood samples taken for the clinical study, a blood sample (~will be collected for the genetic research. The genetic sample is de-identified and labelled (or "coded") with a study specific number. **Coded samples do not carry personal identifiers (such as name or date of birth).**

The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. Per protocol, it is recommended that the

blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for genetic research. Collecting this sample at baseline will reduce the potential for bias between the genetics study population and the clinical study population. In the event that approvals to conduct PGx research are received after study start or that a subject chooses to participate in the genetics sub-study after the randomization visit, the sample may be taken at the next study visit while the subject is participating in the clinical study.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

Aliquots of the sample will be stored securely with GSK and the TIMI Study Group or their agents and may be kept for up to 20 years after the last subject completes the study, except where specified otherwise by local regulations**.** GSK or those working with GSK (for example, other researchers) and the TIMI Study Group will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research and has a sample taken for this research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- The sample is retained for genetic research
- Any genetic sample is destroyed.

If a subject withdraws consent from the genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK and the TIMI Study Group will only keep genetic study information collected/generated up to that point.

Screen Failures

If a blood sample for genetic research has been collected and the subject is not randomized, then the investigator should instruct the participant that his or her genetic sample will be destroyed.

Genetics Analyses

The genetic research conducted may use a variety of genotyping methodologies as needed. For example, specific sections of DNA may be selected from areas of the genome (e.g., candidate genes). In addition, genome-wide scans involving large numbers of polymorphic markers (e.g., single nucleotide polymorphisms (SNPs)) located

throughout the genome may be employed for discovery of novel genetic variants linked to outcomes of interest. Additional methodologies may be used, but only as related the genetic objective stated earlier.

Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease or related cardiovascular disease and, thus, possibly linked to drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance. In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to losmapimod, study treatments and concomitant medications used during the study. The genes that code for these proteins may also be studied.

The candidate genes that may be investigated in this study include, but are not limited to the following:

- SNPs that modify the activity of the carboxylesterase-1 (CES-1) enzyme, an esterase that is involved in the metabolism of losmapimod:

Locus	**SNP**
CES1	rs2244613
CES1	rs8192935
CES1	rs2244613
CES1	rs4122238
CES1	rs8192935

- SNPs encoding proteins that are either directly involved in p38 MAPK signalling or impact the p38 MAPK pathway, including:

Locus	**SNP**
MAPKAPK2	rs4240847
MAPK14	rs916344
RPS6KA4	rs475032
RPS6KA5	rs1286112
RPS6KA5	rs1286076
MAP2K6	rs11656130
MAP2K6	rs2716191

- SNPs linked to disease and to response to standard of care drugs. With statin therapy for example, a SNP in KIF6 (Trp to Arg substitution of the mature protein, Trp719Arg) has been reported to be associated with response to statin treatment [Iakoubova, 2008]. Likewise low density lipoprotein levels are lowered by statins and since SNPs in these genes are linked to study disease [Iakoubova, 2008] these SNPs may have relevance to statin treatment in combination with investigational product. For antiplatelet therapy, SNPs in CYP450 genes and the intestinal efflux pump P-gp have been reported to be linked to attenuated PK, PD and clinical response to clopidogrel [Tantry, 2011].

- Genome-wide scans involving large numbers of polymorphic markers (e.g., single nucleotide polymorphisms or SNPs) located throughout the genome. This approach is often employed for discovery of novel genetic variants linked to outcomes of interest.

If applicable and genetics research is conducted, appropriate statistical analysis methods will be used to evaluate the data in the context of the other clinical data. Results of the genetics investigations will be reported either as part of the main clinical study report or as a separate report. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate genetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the clinical study. Genetics informed consent must be obtained prior to any blood being taken for genetic research.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetics research results in the clinical study report, or separately. In addition, the results may be published in scientific journals. These results will be reported only as summary results for the relevant populations. Individual subject's genetic data will not be tabulated.

Neither the investigator nor the subjects, nor anyone else (e.g., family members, primary care physicians, insurers, or employers) will be informed of the genetics research results from this study because the information generated from genetics studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstances unless required by law. GSK and TIMI may share the results with other scientists to replicate the findings or to further understanding of drug response or cardiovascular disease and related diseases or conditions.

References

Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. J Am Coll Cardiol 2008; 51: 435-443.

Tantry US, Kereiakes DJ, Gurbel PA. Clopidogrel and proton pump inhibitors: influence of pharmacological interactions on clinical outcomes and mechanistic explanations. JACC Cardiovasc Interv 2011; 4: 365-380.

11.5. Appendix 5: Cardiovascular Biomarkers

Background

Cardiovascular biomarkers have proven to play a pivotal role in the evaluation and treatment of patients with atherosclerotic vascular disease [Morrow, 2003a; Morrow, 2007a]. Circulating biomarkers may be used to facilitate diagnosis, enhance risk assessment, monitor disease progression, and to direct therapeutic decision-making [Morrow, 2007a]. In particular, combining multiple biomarkers that reflect distinct pathobiologic contributors to atherothrombosis enhances prognostic assessment [Sabatine, 2002]. Nevertheless, the adoption of multimarker strategies for guiding therapy has been slow; in large part, due to the lack of effective therapies targeted at non-thrombotic and non-lipid targets in patients with atherothrombosis. Although the usefulness of the inflammatory biomarker C-reactive protein (CRP) for selecting patients likely to benefit substantially from statin therapy has shown promise for such strategies [Ridker, 2005; Ridker, 2008], the emergence of novel therapies that target specific inflammatory axes of atherothrombosis has potential to dramatically accelerate such application.

Losmapimod reduces inflammation through the selective inhibition of p38 mitogen activated protein kinase (MAPK). The MAPK signal transduction pathway controls the intracellular signaling for a variety of cellular processes in multiple cell lines including cardiac myocytes, vascular endothelial cells, smooth muscle, and activated macrophages [Johnson, 2002; Kyriakis, 2001]. *In vitro* studies indicate that inhibition of the p38 MAPK pathway with losmapimod reduces the production of inflammatory mediators (GM-CSF), cytokines (TNF-α, IL-1β, IL-6, IL-8) and profibrotic growth factors such as TGF-β [Hu, 2008]. Furthermore, clinical studies have provided evidence that losmapimod has in vivo effects on the inflammatory system as noted by reductions in HSP-27, a downstream target of the p38 pathway. In a study of patients with COPD, treatment with losmapimod resulted in a trend toward decreases in myeloperoxidase, IL-6, IL-8, MMP-9 and hsCRP [Lomas, 2012]. Studies with losmapimod in patients with acute coronary syndrome (ACS) have also provided evidence that p38 MAPK inhibition may have a variety of effects on including attenuating the acute rise in hsCRP, myeloperoxidase, as well as of B-type natriuretic peptide.

Biomarkers and the Pathobiology of Atherothrombosis

The extensive experimental, translational, and clinical investigation elucidating the inflammatory pathobiology of atherothrombosis has fostered a steady pace of emergence of candidate novel cardiovascular biomarkers [Morrow, 2007b]. Such biomarkers include metalloproteinases, (enzymes that disrupt the integrity of the atheroma's protective cap) [Libby, 1995], myeloperoxidase (a potential participant in oxidative injury during atherogenesis), and vascular growth factors such as placental growth factor and soluble Flt-1 [Heeschen, 2004]. As well, non-specific inflammatory biomarkers have a strong base of evidence for interactions with potentially anti-inflammatory interventions. For example, hsCRP has emerged as a convenient tool for detecting low-level systemic inflammation that portends a poor short and long-term prognosis in patients with a

history of definite atherothrombosis and a benefit of intensive statin therapy [Ridker , 1998; Morrow, 2006; Sabatine, 2007].

Other biomarkers may reflect the interplay between inflammatory processes and thrombus generation, such as soluble CD40 ligand, (a marker of platelet activation and potential direct participant in plaque destabilization) [Heeschen, 2003], or with the evolution of myocardial reperfusion injury and adverse remodeling, such as ST2 [Shimpo, 2004; Sabatine, 2008; Kohli, 2012] and growth differentiation factor-15 (GDF15) [Kempf, 2007a; Kempf, 2007b; Wollert, 2007; Bonaca, 2011]. In addition, biomarkers that reflect the downstream consequences of inflammatory injury may also provide complementary information toward risk assessment as well as guiding and assessing the clinical impact of anti-inflammatory therapies. The natriuretic peptides are among the best studied of this category. BNP and NT-proBNP have now been also shown to act as robust predictors of the short and long-term risk of cardiovascular death across the spectrum of ACS[de Lemos, 2001; Morrow, 2003b; Morrow, 2005], as well as in patients with stable ischemic heart disease [Kragelund, 2005]. In addition, mid-regional adrenomedullin and mid-region pro-atrial natriuretic peptide have proven to be equal or superior to natriuretic peptides for risk stratification [Richards, 1998; Morgenthaler, 2005; Sabatine, 2012]. Each of these discrete and interacting pathways may plausibly be influenced by losmapimod as a mechanism for its potential clinical benefits in mitigating the recrudescence and consequences of ACS.

The LATITUDE-TIMI 60 trial provides a unique opportunity to assess the prognostic performance of expanded multimarker approaches to risk stratification and to evaluate the potential influence of losmapimod on the distinct pathways reflected by these biomarkers, as well as to assess whether losmapimod modifies the risk associated with these potential indicators of cardiovascular pathology, in particular, biomarkers of vascular and myocardial inflammation.

Candidate biomarkers include those listed below. Other markers of these processes may be added or substituted as new evidence comes to light.

Biomarkers of Inflammation and Atherogenesis

hs-CRP; Metalloproteinases: PAPP-A, MMP-9, MMP-11; Cathepsins; Myeloperoxidase; Cytokines: IL-1β, IL-1Ra, IL-6, IL-8, IL-18, TNF-α; Chemotactic molecules: MCP-1, CCR1 and CCR2; Placental growth factor and soluble Flt-1; Growth differentiation factor-15; TGF-β; fibroblast growth factor-23; galectin-3; GM-CSF.

Biomarkers of Endothelial Function

vWF, E-selectin, VCAM, ICAM-1

Biomarkers of Thrombosis

sCD40L, tissue factor.

Biomarkers of Oxidative Stress

Oxidized amino acids, oxidized apoA1, ADMA and other arginine metabolism products, secretory phospholipase, $LpPLA_2$.

Biomarkers of Ischemia/Necrosis

High-sensitivity cardiac troponin, micro-RNA.

Biomarkers of Hemodynamic Stress

BNP/NTproBNP, ST-2, copeptin, MRproADM, MRproANP, and NP fragments.

Biomarkers of Metabolic/Lipid Dysregulation

Adiponectin.

Biomarkers of Renal Dysfunction

Cystatin-C, KIM-1, NGAL.

Objectives

1. To evaluate the prognostic performance of baseline assessment of established and novel serum/plasma makers of inflammation, endothelial function, hemodynamic stress, thrombosis, renal dysfunction, and myocardial injury with clinical outcomes at 12 and 24 weeks after presentation with an acute coronary syndrome (ACS).
2. To evaluate the interaction between baseline biomarkers of inflammation, thrombosis, atherogenesis, hemodynamic stress, and myocardial injury with the clinical efficacy of losmapimod.
3. To evaluate the effect of losmapimod on levels of biomarkers of inflammation, endothelial function, thrombosis, atherogenesis, hemodynamic stress, and myocardial injury at 12 weeks after ACS.
4. To assess the change in these biomarkers at 12 weeks and the relationship between the change and subsequent outcomes through 24 weeks.

Study Procedures

1. Blood samples will be collected at baseline, 4 weeks, 12 and 24 weeks in all subjects, where applicable.
2. Plasma/serum are isolated on site & stored until shipped to the central lab.
3. In addition to analysis of biomarkers of necrosis/ischemia, inflammation, and coagulation listed above, proteomics analysis may be performed to develop and test novel protein markers of inflammation, and vascular and myocardial dysfunction.
4. Samples for biomarker testing will be collected in both Part A and Part B. Samples will be shipped to the Central Laboratory for storage when the sample is collected. At the end of Part A, and then again at the end of Part B, a subset of stored samples will be shipped from Central Laboratory to TIMI for laboratory analyses.

Proposed Statistical Analyses

Biomarker data from the TIMI Clinical Trials Laboratory will be merged with the clinical database for statistical analysis. Analyses will be for exploratory purposes and may occur after the clinical database has been authorized for the analyses of the primary and secondary efficacy endpoints and for safety endpoints at the end of the study. It is not expected that these biomarker results from either Part A or Part B will be included in the clinical study report; instead, biomarker results will be reported in a separate document provided by the TIMI organization.

Correlation between serum/plasma markers and outcomes will be analyzed with the marker data both as continuous and categorical variables. Clinical outcomes examined will include the primary efficacy endpoint, and major secondary endpoint, the composite of CV death, myocardial infarction, or heart failure, as well as each element individually. Analyses will be performed to assess the effect of losmapimod on the change in biomarkers from baseline to 12 weeks. In addition, analyses to test for interaction between the effect of losmapimod and biomarkers at baseline will be performed using stratified analyses as well as Cox regression with the main effects and an interaction term.

References

Bonaca MP, Morrow DA, Braunwald E, Cannon CP, Jiang S, Breher S, Sabatine MS, Kempf T, Wallentin L, Wollert KC. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: Observations from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2011;31:203-210.

de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;345:1014-1021.

Heeschen C, Dimmeler S, Fichtlscherer S, Hamm CW, Berger J, Simoons ML, Zeiher AM. Prognostic value of placental growth factor in patients with acute chest pain. *JAMA*. 2004;291:435-441.

Heeschen C, Dimmeler S, Hamm CW, van den Brand MJ, Boersma E, Zeiher AM, Simoons ML. Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med*. 2003;348:1104-1111.

Hu C, Dandapat A, Sun L, Khan JA, Liu Y, Hermonat PL, Mehta JL. Regulation of TGFbeta1-mediated collagen formation by LOX-1: Studies based on forced overexpression of TGFbeta1 in wild-type and LOX-1 knock-out mouse cardiac fibroblasts. *J Biol Chem*. 2008;283:10226-10231.

Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science*. 2002;298:1911-1912.

Kempf T, Horn-Wichmann R, Brabant G, Peter T, Allhoff T, Klein G, Drexler H, Johnston N, Wallentin L, Wollert KC. Circulating concentrations of growth-differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. *Clin Chem*. 2007a;53:284-91.

Kempf T, von Haehling S, Peter T, Allhoff T, Cicoira M, Doehner W, Ponikowski P, Filippatos GS, Rozentryt P, Drexler H, Anker SD, Wollert KC. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol*. 2007b;50:1054-1060.

Kohli P, Bonaca MP, Kakkar R, Kudinova AY, Scirica BM, Sabatine MS, Murphy SA, Braunwald E, Lee RT, Morrow DA. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. *Clin Chem*. 2012;58:257-266.

Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;352:666-675.

Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. *Physiological reviews*. 2001;81:807-869.

Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844-2850.

Lomas DA, Lipson DA, Miller BE, Willits L, Keene O, Barnacle H, Barnes NC, Tal-Singer R, Losmapimod Study I. An oral inhibitor of p38 map kinase reduces plasma fibrinogen in patients with chronic obstructive pulmonary disease. *J Clin Pharmacol*. 2012;52:416-424.

Morgenthaler NG, Struck J, Alonso C, Bergmann A. Measurement of midregional proadrenomedullin in plasma with an immunoluminometric assay. *Clin Chem*. 2005;51:1823-1829

Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. *Circulation*. 2003a;108:250-252.

Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH. National academy of clinical biochemistry laboratory medicine practice guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation*. 2007b;115:e356-e375.

Morrow DA, de Lemos JA, Blazing MA, Sabatine MS, Murphy SA, Jarolim P, White HD, Fox KA, Califf RM, Braunwald E. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *JAMA*. 2005;294:2866-2871.

Morrow DA, de Lemos JA, Sabatine MS, Murphy SA, Demopoulos L, DiBattiste P, McCabe C, Gibson CM, Cannon CP, Braunwald E. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST elevation MI: BNP and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol*. 2003b;41:1264-1272.

Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor trial. *Circulation*. 2006;114:281-288.

Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation*. 2007a;115:949-952.

Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, Buttimore RC, Lainchbury JG, Elliott JM, Ikram H, Crozier IG, Smyth DW. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: New neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation*. 1998;97:1921-1929.

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352:20-28.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207.

Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) investigators. *Circulation*. 1998;98:839-844.

Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: Simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002;105:1760-1763.

Sabatine MS, Morrow DA, de Lemos JA, Omland T, Sloan S, Jarolim P, Solomon SD, Pfeffer MA, Braunwald E. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation*. 2012;125:233-240.

Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, Rifai N, Cannon CP, Gerszten RE, Lee RT. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. *Circulation*. 2008;117:1936-1944.

Sabatine MS, Morrow DA, Jablonski KA, Rice MM, Warnica JW, Domanski MJ, Hsia J, Gersh BJ, Rifai N, Ridker PM, Pfeffer MA, Braunwald E. Prognostic significance of the Centers For Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. *Circulation*. 2007;115:1528-1536.

Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, Lee RT. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation*. 2004;109:2186-2190.

Wollert KC, Kempf T, Lagerqvist B, Lindahl B, Olofsson S, Allhoff T, Peter T, Siegbahn A, Venge P, Drexler H, Wallentin L. Growth differentiation factor 15 for risk stratification and selection of an invasive treatment strategy in non ST-elevation acute coronary syndrome. *Circulation*. 2007;116:1540-1548.