

Division: Worldwide Development**Information Type:** Protocol Amendment**Title:**

A Clinical Outcomes Study of Darapladib versus Placebo in Subjects Following Acute Coronary Syndrome to Compare the Incidence of Major Adverse Cardiovascular Events (MACE)

(Short title: The Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52 SOLID-TIMI 52 Trial)

Compound Number: SB-480848**Effective Date:** 26-FEB-2014**Protocol Amendment Number:** 05**Subject:** atherosclerosis, Lp-PLA₂ inhibitor, acute coronary syndrome, SB-480848, darapladib**Author:**

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Revision Chronology:

RM2007/00497/01	2009-OCT-08	Original
RM2007/00497/02	2010-NOV-30	<p>Amendment 01: The primary intent is to revise certain inclusion and exclusion criteria. These and other changes are summarized below.</p> <ul style="list-style-type: none">• The Greenford address is deleted from the Sponsor Information Page.• The address and phone number for Dr. Patrick Vallance on the Sponsor Information Page is updated.• The Harlow address and phone number on the Sponsor Information Page is updated.• It is clarified that a PCI planned prior to randomization but performed after randomization is not counted towards the composite measure of total coronary events.• The reference for the guidelines for the management of patients with STEMI is updated in accordance with the latest guidelines issued by the American College of Cardiology/American Heart Association.• For eligibility assessments, local laboratory values obtained from samples collected after the subject signs the ICF may now be used.• In inclusion criterion 2, it is specified that, in Taiwan, subjects must be at least 20 years of age at randomization.• Inclusion criterion 3c is revised to allow a diagnostic elevation in creatine kinase to be included in

the definition of STEMI.

- The statement “Significant renal dysfunction refers to reduced eGFR based on serum creatinine prior to cardiac catheterization or PCI based on local laboratory values.” is deleted from footnote 6.
- In inclusion criterion 4e, it is clarified that polyvascular disease is defined as ACS plus at least one of either cerebrovascular disease or peripheral arterial disease.
- In exclusion criterion 2, it is clarified that “absence of obstructive coronary artery disease” would not include the scenario in which all lesions are successfully treated by PCI.
- In exclusion criterion 4 and footnote 10, the definition of liver disease is revised, AST is removed from the list of required liver function tests, and subjects with chronic stable hepatitis may be enrolled under certain circumstances.
- In footnote 12 for exclusion criterion 7, the requirement to obtain a mean of 3 BP measurements is no longer mandated.
- In footnote 13 for exclusion criterion 13, the list of examples of strong CYP3A4 inhibitors is updated.
- In exclusion criterion 12, the text is revised to clarify that subjects with alcohol or drug abuse within the past 6 months must not be enrolled regardless of the

investigator's assessment regarding the subject's ability to comply with the study requirements.

- In exclusion criterion 14, the plasma Lp-PLA2 activity threshold for excluding subjects of Japanese, Chinese or Korean ancestry is revised from ≤ 10 to ≤ 20.0 nmol/min/mL.
- In footnote 14 for exclusion criterion 14, the reference for effect of the 279F variant on Lp-PLA2 activity is updated.
- Less frequent telephone follow-up in subjects who discontinue IP prior to the end of the study is now allowed.
- It is clarified that clinic visits may be used to collect data specified for telephone visits if desired.
- A new paragraph is added to emphasize the need to review and document all options for subject follow-up before confirming that the subject has withdrawn consent.
- Among the possible reasons for discontinuation of IP, "Sponsor terminated study treatment" is added.
- The description of the randomization number is corrected from a 5- to a 6-digit number
- It is clarified that the first dose of IP should be taken on the day of randomization.
- Expedited SAE reports sent to clinical investigators no longer identify the subject's treatment assignment.

- In the Time and Events Table 1, it is specified that the Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization.
- In the Time and Events Table 2, the modified Rankin Scale and pregnancy test are now optional for unscheduled visits.
- In the Time and Events Table 2, the IVRS call is removed from unscheduled visits.
- In the Time and Events Table 2, footnote 3, it is noted that the End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within the window for collecting the trough Lp-PLA2 activity sample (24 ± 2 hours after the final IP dose) or earlier, and that samples for Lp-PLA2 activity and stored biomarkers are not collected at the Follow-up Visit
- In the Time and Events Table 2, footnote 4, smoking status was included in error and is now deleted from the list of post-randomization full physical exam assessments.
- “All coronary revascularization procedures” is added as an “other” endpoint.
- The phrase “the first occurrence of” is deleted from the “other” endpoint of total vascular events.
- The list of “Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs” is revised to include all

non-fatal strokes.

- It is clarified that the modified Rankin scale is performed in all subjects regardless of stroke history.
- The statement that the treatment effect will be assessed at a nominal 0.05 significance level for the integrated efficacy analyses is deleted.

RM2007/00497/03

2012-APR-26

Amendment No 2: The primary intent is to allow the Follow-up visit to be conducted by telephone in subjects who meet pre-defined criteria. Other changes are summarized below.

- Replace Dr. Patrick Vallance on sponsor signatory and sponsor information pages.
- Update List of Abbreviations and correct format errors.
- Revise text regarding scheduling of the End of Treatment visit.
- Clarify that publically available information may be used to report endpoints/survival status in subjects who withdraw consent to participate in the study.
- Remove requirement for investigators to contact the sponsor prior to restarting IP in subjects who have been off IP for more than 1 month.
- Provide guidance to investigational sites regarding recording the non-adjudicated endpoint “hospitalization for non-coronary ischemic event” in Section 6.3.3.
- Edit text in Section 6.4.1 (Liver

chemistry stopping and follow-up criteria) for improved consistency with algorithm in Appendix 7 (Liver Chemistry Stopping and Follow-up Criteria).

- Edit text in Section 6.4.3 (Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs) to clarify definition of Hy's law.
- Allow restarting of IP in certain subjects who met liver stopping criteria.

RM2007/00497/04

2012-OCT-22

Amendment No.: 03 - The primary intent is to allow increased collection of data on new cancer, recurrence of cancer, or progression of cancer; and adjudication of all gastrointestinal (GI) neoplasms (malignant and benign), and all GI polyps (malignant, benign, and non-neoplastic). Other changes are summarized below.

- Add PRIMARY CONTACTS FOR EXTERNAL COMMITTEES WITH OVERSIGHT OR ADMINISTRATIVE RESPONSIBILITIES. This information was inadvertently omitted from previous protocol amendment (Amendment #2).
- Request a final clinic visit for subjects who permanently discontinued IP prior to the end of the study.
- Correct text to be consistent regarding use of telephone and clinic visits to follow subjects who permanently discontinue IP prior to the end of the study.
- Clarify data collection for subjects who have discontinued IP and are

in post-IP follow-up.

- Allow a subject who met liver chemistry stopping criteria to restart IP if liver chemistries have improved to within the normal range, even if >1.5 x Baseline.
- Clarify completion of Follow-up checklist for subjects who withdrew consent for participation in the study.

RM2007/00497/05	2012-NOV-29	Amendment No.: 04 – This country-specific amendment for France is required by the French regulatory authority (ANSM). Subjects diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis) must immediately discontinue investigational product (IP).
RM2007/00497/06	2014-FEB-26	Amendment No.: 05 The primary reason for this amendment is to change the primary efficacy endpoint from Major Adverse Cardiovascular Events (MACE: cardiovascular death, non-fatal MI, or non-fatal stroke) to the previous secondary endpoint of Major Coronary Events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia). Additional changes have been made to secondary and “other” endpoints to reflect the change to the primary endpoint (see rationale in Section 11.11.)

Sponsor Signatory:**Signature:****Date:**

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission

Regulatory Agency Identifying Number(s):

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INVESTIGATOR AGREEMENT PAGE

For protocol SB-480848/033

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. 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

ACEi	Angiotensin Converting Enzyme inhibitor
ACR	Albumin:Creatinine Ratio
ACS	Acute Coronary Syndrome
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration vs. Time Curve
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CEC	Clinical Endpoint Committee
CHD	Coronary Heart Disease
CI	Confidence Interval
CK-MB	Creatine Kinase Muscle-Brain isozyme
Cmax	Maximum drug concentration
CPK	Creatinine Phosphokinase
CT scan	Computed Tomography scan
CV	Cardiovascular
CYP3A4	Cytochrome P-450 isoenzyme 3A4
DBP	Diastolic Blood Pressure
dL	Deciliter
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
EudraCT	European Drug Regulatory Authorities Clinical Trials
EW	Early Withdrawal
FDA	US Food and Drug Administration
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour
HbA1c	Hemoglobin subtype A1c
HBsAg	Hepatitis B surface Antigen
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-Reactive Protein
hCG	human Chorionic Gonadotropin
IBIS	Integrated Biomarker and Imaging Study

ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL-6	Interleukin-6
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IVUS	Intravascular Ultrasound
kg	Kilogram
L	Liter
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
Lp-PLA ₂	Lipoprotein-Associated Phospholipase A ₂
LVH	Left Ventricular Hypertrophy
Lyso-PC	Lysophosphatidyl Choline
LYS	Life Years Saved
MACE	Major Adverse Cardiovascular Events
MDRD equation	Modification of Diet in Renal Disease equation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
mg	Milligram
mL	Milliliter
mm Hg	Millimeters of mercury
mmol	Millimole
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
msec	Millisecond
NEFA	Non-Esterified Fatty Acid
nmol	nanomole
NONMEM	Nonlinear Mixed Effects Modeling
NSTEMI	Non-ST segment Elevation Myocardial Infarction
NYHA	New York Heart Association
ng	Nanogram
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic(s)
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
QALY	Quality-Adjusted Life Years
RAMOS	Registration and Medication Ordering System

RAP	Reporting and Analysis Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMS	Short Messaging Service
SNP	Single-Nucleotide Polymorphism
SOM	Site Operations Manual
STEMI	ST segment Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
Tmax	Time of maximal plasma concentration
UA	Unstable Angina
ULN	Upper Limit of Normal (reference range for laboratory)
µmol	Micromole
URL	Upper Reference Limit
US/USA	United States of America

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PROTOCOL SUMMARY

Rationale

Why Lp-PLA₂ inhibition?

Elevated plasma levels of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) are associated with an increased risk of cardiovascular (CV) events [Garza, 2007]. The majority of published studies in primary and secondary prevention populations confirm an association between the levels of Lp-PLA₂ and the risk of CV events that is independent of conventional risk factors. Epidemiologic studies in patients with prevalent coronary heart disease (CHD) were conducted in those with chronic CHD and those with post-acute coronary syndrome (ACS) [Corsetti, 2006; Koenig, 2006; O'Donoghue, 2006; Brilakis, 2006].

Lp-PLA₂ is the product of activated inflammatory cells (e.g., monocyte-derived macrophages, T cells, mast cells) with circulating Lp-PLA₂ predominantly bound to low-density lipoprotein cholesterol (LDL-C) [Zalewski, 2005]. Enzymatic activity of Lp-PLA₂ results in production of the pro-inflammatory and pro-apoptotic mediators lysophosphatidyl choline (lyso-PC) and oxidized non-esterified fatty acids (NEFAs) from oxidized LDL-C [Carpenter, 2001; Hsieh, 2000; Macphee, 1999; Shi, 2007b; Takahashi, 2002] which may account for part of the vascular inflammation associated with oxidized LDL-C. High expression of Lp-PLA₂ has also been noted in human atherosclerotic lesions, particularly in thin cap fibroatheroma or ruptured plaques [Häkkinen, 1999; Kolodgie, 2006]. In these high risk lesions that often lead to sudden death or myocardial infarction (MI), the enzyme is highly localized to activated macrophages undergoing apoptosis in the lipid necrotic core and fibrous cap, which suggests a potential role in promoting plaque instability [Kolodgie, 2006]. Selective inhibition of plasma and lesion Lp-PLA₂ activity was shown to inhibit progression to advanced coronary atherosclerotic lesions in diabetic and hypercholesterolemic swine [Wilensky, 2008]. Therefore, inhibition of Lp-PLA₂ may reduce vascular inflammation and promote stability of atherosclerotic plaques in patients with CHD.

Target Patient Population

ACS – underlying pathology: ACS represents a spectrum of clinical presentations (unstable angina [UA], non-ST segment elevation MI [NSTEMI], ST segment elevation MI [STEMI]) that are associated with an increased risk of CV death, non-fatal MI and recurrent hospital admissions for refractory myocardial ischemia. The rupture of a thin cap fibroatheroma or plaque fissuring, resulting in luminal thrombus formation, are the most common underlying causes of ACS [Falk, 2006; Virmani, 2000]. Current treatments in ACS are directed at achieving rapid relief of myocardial ischemia with antiplatelet and antithrombotic agents combined with early revascularization of the culprit lesion in the appropriate patients [Held, 2007; Mehta, 2005; Anderson, 2007; Bassand, 2007]. It is notable, however, that these patients have an increased systemic inflammatory state often combined with the presence of multifocal plaque vulnerability throughout the coronary vasculature [Buffon, 2002; Rioufol, 2002; Spagnoli, 2002; Hong, 2004]. Recent clinical

trials confirm high residual risk of recurrent CV events in post-ACS patients that persists despite aggressive in-hospital management of the culprit lesion and the post-discharge chronic therapies [Cannon, 2004; de Lemos, 2004; Ray, 2005]. The results of large outcomes trials highlighted that greater anti-inflammatory effects achieved with statins are associated with improved clinical outcomes [Ridker, 2005; Morrow, 2006]. Further comparisons of large trials (MIRACL, A-to-Z, and PROVE IT-TIMI 22) suggest that LDL-C lowering alone without the concomitant anti-inflammatory effect may result in a less effective clinical strategy in this high risk population [Ray, 2005]. These results illustrate the therapeutic potential of a more specific anti-inflammatory approach that targets plaque by means of Lp-PLA₂ inhibition when added to standard of care.

ACS – and Lp-PLA₂ levels: As noted above, high risk human coronary lesions that are responsible for the majority of fatal myocardial infarctions over-express Lp-PLA₂ [Kolodgie, 2006]. Nevertheless, circulating levels of this enzyme are difficult to interpret during the early phase of ACS. To this end, studies that measured plasma Lp-PLA₂ (mass or activity) within the first few days after the onset of ACS showed no correlation with subsequent CV events [O'Donoghue, 2006; Oldgren, 2007]. This finding is likely due to a transient drop in the levels of its carrier, LDL-C, in higher risk ACS patients [Kinlay, 2003]. In fact, when the measurements of Lp-PLA₂ are carried out later (e.g., ≥30 days), Lp-PLA₂ levels become independent predictors of the subsequent CV events [Corsetti, 2006; Koenig, 2006; O'Donoghue, 2006]. These observations highlight that unlike troponins, high sensitivity C-reactive protein (hsCRP) or brain natriuretic peptide (BNP) measurements, circulating Lp-PLA₂ is not a sensitive prognostic marker in the early phase of ACS. In contrast to these markers, Lp-PLA₂ exerts specific pro-inflammatory and pro-apoptotic intra-plaque effects, thus providing the rationale for testing whether its inhibition in atherosclerotic lesions will translate into long-term benefit in high risk post-ACS patients regardless of plasma levels.

ACS – and unmet medical needs: Despite implementation of several in-hospital interventions (e.g., antiplatelet and antithrombotic therapies combined with urgent coronary revascularization) with several of them continued chronically post-discharge (e.g., antiplatelet agents, statins, angiotensin converting enzyme inhibitors [ACEi], β-blockers), the results of the PROVE IT-TIMI 22 trial clearly illustrated high residual risk that persists in post-ACS patients. To this end, 22% of patients randomized within the first 10 days of the presentation to daily doses of atorvastatin 80 mg experienced death or major CV events over the median 2 years of therapy in spite of achieving mean LDL-C levels of 62 mg/dL (1.60 mmol/L) [Cannon, 2004]. Several clinical and laboratory characteristics identify those patients who are at greater risk of death or recurrent ischemic event. They include those ACS patients who exhibit at least one of the following additional criteria: age >65 years (or potentially younger in developing countries [Xavier, 2008]), diabetes mellitus, presence of multiple risk factors, chronic kidney disease, or those with documented non-coronary vascular disease [de Araujo Goncalves, 2005; Al Suwaidi, 2002; Anavekar, 2004; Norhammar, 2004]. Of note, these high risk ACS patients constitute approximately 50-80% of the entire population of ACS and paradoxically receive less intensive therapy [Alexander, 2005; Rosengren, 2006; Wright, 2002; Yan, 2006].

Summary

Based on the emerging epidemiologic association between Lp-PLA₂ and CV events, as well as the proposed role of this enzyme in the formation of putative mediators of plaque instability and its high expression in vulnerable plaques, it is postulated that the direct inhibition of this pro-inflammatory enzyme may provide therapeutic benefits in CV patients.

Previous clinical studies of darapladib (SB-480848), a novel Lp-PLA₂ inhibitor in development for CV risk reduction, have shown dose-dependent inhibition of intra-plaque (2 weeks of dosing) and plasma Lp-PLA₂ activity (up to 12 weeks of dosing) [Johnson, 2004; Shi, 2007a; Mohler, 2008]. In addition, in a study of high risk chronic CHD and ACS patients examined by intravascular ultrasound (IVUS)-based imaging, once daily doses of Darapladib Enteric Coated Tablets, 160 mg given for 1 year halted progression of the necrotic core. Sustained inhibition of Lp-PLA₂ activity was observed throughout 1 year in the darapladib-treated group [Serruys, 2008].

This Phase III outcome study was initially designed to compare the chronic effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care ≤ 30 days following presentation, on the incidence of major adverse cardiovascular events (MACE) in high risk patients following ACS. Prior to unblinding the study data, the primary endpoint of the study was amended and replaced with the secondary endpoint of major coronary events (i.e., CHD death, non-fatal MI, urgent coronary revascularization for myocardial ischemia). Conduct of the study was based on the original primary endpoint of MACE.

Rationale for change to primary efficacy endpoint

The Executive Steering Committee of the ongoing SOLID-TIMI-52 trial met to review data from the STABILITY (Study LPL100601) trial (similar design as Study SB-480848/033 except in a chronic CHD population) and made the recommendation to GSK that the primary endpoint of the SOLID-TIMI-52 trial (Study SB-480848/033) be revised to Major Coronary Events (CHD death, non-fatal myocardial infarction and urgent coronary revascularization for myocardial ischemia) from MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke). Specifically, this change would primarily remove both fatal and non-fatal stroke from the composite endpoint. In addition, emerging data from genetic studies and epidemiologic data show a lack of association between Lp-PLA₂ activity and risk of stroke. **The decision by GSK to follow the Executive Steering Committee's recommendation to amend the primary endpoint of the SOLID-TIMI 52 study was made prior to unblinding study data and without communication from the IDMC.**

Objective(s)

Primary objective:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia).

Secondary objectives:

The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters, including relations to and changes of biomarkers of CV risk, genetics, health economic outcomes, and adverse events (AEs), will also be evaluated.

Study Design

The primary endpoint of the study was amended prior to unblinding the study data. Conduct of the study was based on the original primary endpoint of MACE. Data collection in the study was not affected by this change since the new primary endpoint was previously a secondary endpoint.

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event-driven trial. Subjects with ACS and receiving standard of care will be randomized 1:1 to once daily doses of Darapladib Enteric Coated Tablets, 160 mg or placebo. The duration of the study will be determined by the rate of first occurrence of events that comprise the MACE composite. The study will be terminated when approximately 1500 reports of first occurrence of MACE have occurred. Based on current assumptions, it is anticipated that most subjects will be dosed for a minimum of 2 years (except for those who permanently discontinue investigational product or die) and up to 4.1 years or more. Median treatment duration is anticipated to be approximately 3 years.

It is projected that the study will screen approximately 14,500 subjects with ACS in order to randomize a minimum of approximately 11,500 total subjects, or at least 5750 subjects per treatment arm. It is planned that subject accrual will occur across a minimum of approximately 900 sites worldwide over a minimum period of approximately 24 months.

All subjects are to be followed until the termination of the study, regardless of whether they permanently discontinue treatment with investigational product (IP) or experience a

non-fatal MACE. Ideally, subjects will continue treatment with IP after experiencing a MACE.

Study Endpoints/Assessments

The primary endpoint is the time to the first occurrence of any component of the composite of **major coronary events** that include CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia in an ACS patient population.

Secondary endpoints include:

- The composite measure of **MACE** that includes CV death, non-fatal MI, or non-fatal stroke.
- **Individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]).
- **Individual components of major coronary events** (CHD death, MI [fatal and non-fatal], urgent coronary revascularization for myocardial ischemia).
- The composite measure of **total coronary events** that include CHD death, non-fatal MI, hospitalization for UA, or any coronary revascularization procedure (excluding percutaneous coronary intervention [PCI] planned prior to randomization but performed after randomization).
- Any coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).
- Any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- The composite of CHD death and non-fatal MI
- All cause mortality.

Blood samples for clinical laboratory tests and Lp-PLA₂ activity will be collected at Baseline and at several time points post-randomization. Blood samples for assay of circulating biomarkers of CV risk will also be collected in all subjects at Baseline and thereafter at various time points and stored for future analysis. Blood samples for genetic and pharmacokinetic analyses will also be collected in a subset of subjects as described in [Appendix 6](#) and [Appendix 8](#).

Vital signs, electrocardiograms (ECGs), clinical laboratory safety tests and AE assessments will be performed to evaluate the safety and tolerability of darapladib.

1. INTRODUCTION

1.1. Background

Population description

Acute coronary syndrome (ACS) represents a spectrum of clinical presentations (unstable angina [UA], non-ST segment elevation myocardial infarction [NSTEMI], ST segment elevation myocardial infarction [STEMI]) that are associated with an increased risk of cardiovascular (CV) death, non-fatal myocardial infarction (MI) and recurrent hospital admissions for refractory myocardial ischemia. The rupture of a thin cap fibroatheroma or plaque fissuring, resulting in luminal thrombus formation, are the most common underlying causes of ACS [Falk, 2006; Virmani, 2000]. Current treatments in ACS are directed at achieving rapid relief of myocardial ischemia with antiplatelet, antithrombotic agents combined with early revascularization of the culprit lesion in the appropriate patients [Held, 2007; Mehta, 2005; Anderson, 2007; Bassand, 2007]. It is notable, however, that these patients have an increased systemic inflammatory state often combined with the presence of multifocal plaque vulnerability throughout the coronary vasculature [Buffon, 2002; Rioufol, 2002; Spagnoli, 2002; Hong, 2004]. Recent clinical trials confirm high residual risk of recurrent CV events in post-ACS patients that persists despite aggressive in-hospital management of the culprit lesion and the post-discharge chronic therapies [Cannon, 2004; de Lemos, 2004; Ray, 2005]. The results of large outcomes trials highlighted that greater anti-inflammatory effects achieved with statins are associated with improved clinical outcomes [Ridker, 2005; Morrow, 2006]. Further comparisons of large trials (MIRACL, A-to-Z, and PROVE IT-TIMI 22) suggest that low-density lipoprotein cholesterol (LDL-C) lowering alone without the concomitant anti-inflammatory effect may result in a less effective clinical strategy in this high risk population [Ray, 2005]. These results illustrate the therapeutic potential of a more specific anti-inflammatory approach by means of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) inhibition when added to standard of care.

Need for new therapy for ACS

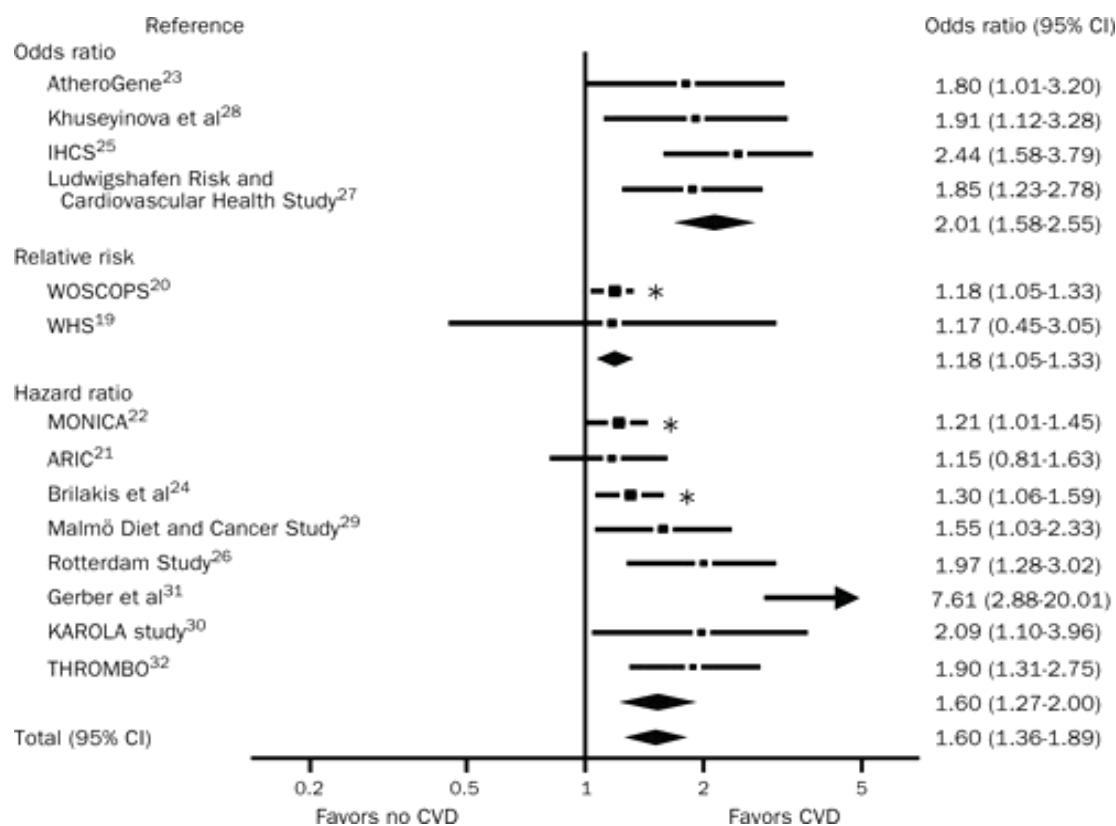
Despite implementation of several in-hospital interventions (e.g., antiplatelet and antithrombotic therapies combined with urgent coronary revascularization) with several of them continued chronically post-discharge (e.g., antiplatelet agents, statins, angiotensin converting enzyme inhibitors [ACEi], β-blockers), the results of PROVE IT-TIMI 22 trial clearly illustrated high residual risk that persists in post-ACS patients. To this end, 22% of patients randomized within the first 10 days of the presentation to daily doses of atorvastatin 80 mg experienced death or major CV events over the median 2 years of therapy in spite of achieving mean LDL-C levels of 62 mg/dL [Cannon, 2004]. Several clinical and laboratory characteristics identify those patients who are at greater risk of death or recurrent ischemic event. They include those ACS patients who exhibit at least one of the following additional criteria: age >65 years (or potentially younger in developing countries [Xavier, 2008]), diabetes mellitus, presence of multiple risk factors, chronic kidney disease, multivessel CHD, or those with

documented non-coronary vascular disease [de Araujo Goncalves, 2005; Al Suwaidi, 2002; Anavekar, 2004; Norhammar, 2004]. Of note, these high risk ACS patients constitute approximately 50-80% of the entire population of ACS and paradoxically receive less intensive therapy [Alexander, 2005; Rosengren, 2006; Wright, 2002; Yan, 2006].

Lp-PLA₂ inhibition as a new therapeutic strategy to further reduce risk of CV events

As shown in Figure 1 [Garza, 2007], elevated plasma levels of Lp-PLA₂ are associated with an increased risk of CV events. Most published studies in primary and secondary prevention populations confirm an association between the levels of Lp-PLA₂ and the risk of CV events that is independent of conventional risk factors. Epidemiologic studies in patients with prevalent CHD were conducted in those with chronic CHD and those with post-ACS [Corsetti, 2006; Koenig, 2006; O'Donoghue, 2006; Brilakis, 2006].

Figure 1 Meta-analysis of Lp-PLA₂ association with CV disease (adjusted for conventional risk factors)



Lp-PLA₂ is the product of activated inflammatory cells (e.g., monocyte-derived macrophages, T cells, mast cells) with circulating Lp-PLA₂ predominantly bound to LDL-C [Zalewski, 2005]. Enzymatic activity of Lp-PLA₂ results in production of the pro-inflammatory and pro-apoptotic mediators lysophosphatidyl choline (lyso-PC) and oxidized nonesterified fatty acids (NEFAs) from oxidized LDL-C [Carpenter, 2001; Hsieh, 2000; Macphee, 1999; Shi, 2007b; Takahashi, 2002] which may account for part of the vascular inflammation associated with oxidized LDL-C. High expression of Lp-PLA₂ has been noted in human atherosclerotic lesions, particularly in thin cap fibroatheroma or ruptured plaques [Häkkinen, 1999; Kolodgie, 2006]. In these high risk lesions that often lead to sudden death or MI, the enzyme is highly localized to activated macrophages undergoing apoptosis in the lipid necrotic core and fibrous cap which suggests a potential role in promoting plaque instability [Kolodgie, 2006]. Selective inhibition of plasma and lesion Lp-PLA₂ activity was shown to inhibit progression to advanced coronary atherosclerotic lesions in diabetic and hypercholesterolemic swine [Wilensky, 2008]. Therefore, inhibition of Lp-PLA₂ may reduce vascular inflammation and promote stability of vulnerable plaques in patients with CHD.

Darapladib (SB-480848)

Darapladib is a novel, selective, reversible, orally active inhibitor of Lp-PLA₂ activity in development by GlaxoSmithKline (GSK) for CV risk reduction. Refer to the Investigator's Brochure for further information on darapladib (See Site Operations Manual [SOM] for current version of the Investigator's Brochure).

1.2. Rationale

Based on the emerging epidemiologic association between Lp-PLA₂ and CV events, as well as the proposed role of this enzyme in the formation of putative mediators of plaque instability and its high expression in vulnerable plaques, it is postulated that the direct inhibition of this pro-inflammatory enzyme may provide therapeutic benefits in CV patients.

Previous clinical studies of darapladib (SB-480848), a novel Lp-PLA₂ inhibitor in development for CV risk reduction, have shown dose-dependent inhibition of intra-plaque (2 weeks of dosing) and plasma Lp-PLA₂ activity (up to 12 weeks of dosing) [Johnson, 2004; Shi, 2007a; Mohler, 2008]. In addition, in a study of high risk chronic CHD and ACS patients examined by intravascular ultrasound (IVUS)-based imaging, once daily doses of Darapladib Enteric Coated Tablets, 160 mg given for 1 year halted progression of the necrotic core. Sustained inhibition of Lp-PLA₂ activity was observed throughout 1 year in the darapladib-treated group [Serruys, 2008].

This Phase III outcome study was initially designed to compare the chronic effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care ≤ 30 days following presentation, on the incidence of major adverse cardiovascular events (MACE) in high risk patients following ACS. Prior to unblinding the study data, the primary endpoint of the study was amended and replaced with the secondary endpoint of major coronary events (i.e., CHD death, non-fatal MI, urgent

coronary revascularization for myocardial ischemia). Conduct of the study was based on the original primary endpoint of MACE.

Rationale for change to primary efficacy endpoint

The Executive Steering Committee of the ongoing SOLID-TIMI-52 trial met to review data from the STABILITY (Study LPL100601) trial (similar design as Study SB-480848/033 except in a chronic CHD population) and made the recommendation to GSK that the primary endpoint of the SOLID-TIMI-52 trial (Study SB-480848/033) be revised to Major Coronary Events (CHD death, non-fatal myocardial infarction and urgent coronary revascularization for myocardial ischemia) from MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke). Specifically, this change would primarily remove both fatal and non-fatal stroke from the composite endpoint. In addition, emerging data from genetic studies and epidemiologic data show a lack of association between Lp-PLA₂ activity and risk of stroke. **The decision by GSK to follow the Executive Steering Committee's recommendation to amend the primary endpoint of the SOLID-TIMI 52 study was made prior to unblinding study data and without communication from the IDMC.**

2. OBJECTIVE(S)

Primary objective:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia).

Secondary objectives:

The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters, including relations to and changes of biomarkers of CV risk, health economic outcomes, and adverse events (AEs), will also be evaluated.

3. INVESTIGATIONAL PLAN

This section describes the study design and the organization of the trial. See the accompanying SOM for supplementary information on the conduct of this trial not

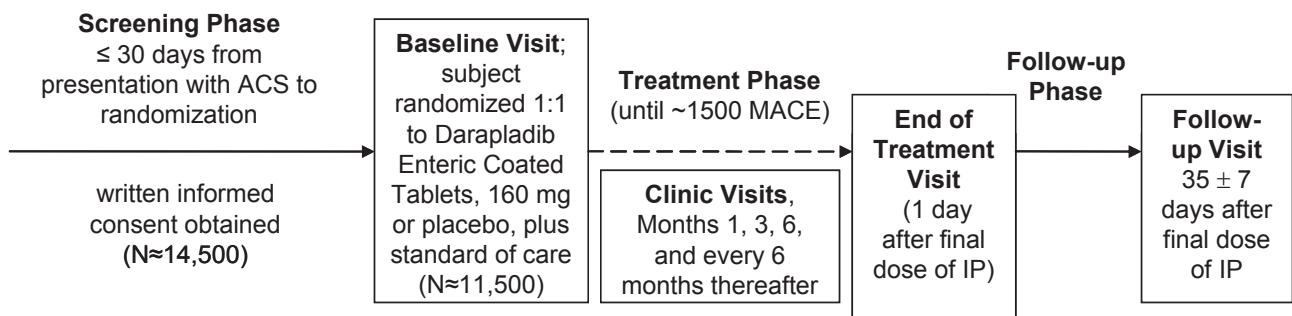
mandated to be present in this protocol. The SOM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.1. Study Design

The primary endpoint of the study was amended prior to unblinding the study data. Conduct of the study was based on the original primary endpoint of MACE. Data collection in the study was not affected by this change since the new primary endpoint was previously a secondary endpoint.

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event driven trial (See [Figure 2](#)). The duration of the study will be determined by the rate of first occurrence of clinical events that comprise the composite of MACE. The study will be terminated when it is projected that approximately 1500 reports of first occurrence of MACE have occurred. Based on current assumptions, the median treatment duration is anticipated to be approximately 3 years.

All subjects are to be followed until the termination of the study, regardless of whether they permanently discontinue treatment with investigational product (IP) or experience a non-fatal MACE. Ideally, subjects will continue treatment with IP after experiencing a MACE.

Figure 2 Study Design

Screening Phase

Written informed consent must be obtained from each subject prior to participation in the study. The Screening Phase begins when written informed consent is obtained from the subject and ends at randomization. The subject must be randomized \leq 30 days following presentation with ACS.

A subject presenting with ACS, including UA, NSTEMI or STEMI, will be treated at the discretion of their physician. During the Screening Phase, the subject should be started and/or continued on the standard of care for ACS during in-hospital treatment and after hospital discharge according to local professional guidelines for secondary prevention patient population [Smith, 2006; Anderson, 2007; Kushner, 2009; Bassand, 2007; Van de Werf, 2008]. It is expected that approximately 50% of the total study population will have undergone coronary revascularization (i.e., percutaneous coronary intervention [PCI]) prior to randomization, consistent with current therapeutic guidelines for high risk ACS patients.

A screening log electronic case report form (eCRF) must be completed for every subject with a signed informed consent form (ICF). Each subject who signs the ICF must be registered in the Registration and Medication Ordering System (RAMOS) interactive voice response system (IVRS).

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 were done before randomization, the results of these procedures may be used to complete the screening log eCRF. (NOTE: The Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization.) The subject does not need to repeat recently completed procedures/tests for study qualification (including laboratory tests). For such subjects, the study qualification procedures should be abbreviated and it is possible to combine the study qualification and randomization into a single visit. Any protocol-specified study qualification procedures/tests not already done as part of routine care will need to be conducted after the subject signs the ICF and before randomization. All subjects must sign the ICF before any study-specific procedure including randomization.

Study qualification criteria that involve laboratory results may be based on local laboratory values obtained \leq 8 weeks prior to randomization (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during the qualifying hospitalization) and prior to the subject signing the ICF. If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **NOTE: For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization \leq 30 days following hospitalization for ACS.**

For subjects who did not have any protocol-specified study qualification procedures done as part of routine care before randomization, the following study qualification procedures must be completed to ensure that the subject is eligible for the study.

- Sign ICF.
- Review inclusion/exclusion criteria.
- Ensure that the subject qualifies with regard to the following laboratory tests for exclusion criteria:
 - Liver function assessments (alanine aminotransferase [ALT], alkaline phosphatase, bilirubin).
 - Renal function (estimated glomerular filtration rate [eGFR]).
 - Lp-PLA₂ activity for subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry).

Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the laboratory values were obtained ≤ 8 weeks before randomization. Alternatively, the central laboratory may be utilized for the above study qualification laboratory tests. Beginning with the Baseline Visit, the central laboratory must be used for all protocol-specified laboratory tests.

- Review concomitant medications for assessment of exclusion criteria.
- Call the IVRS to register the subject for the study.

Full source documentation for the above qualifying procedures and related results are required even if local laboratory results (within the previous 8 weeks) were used to qualify the subject. Therefore, a screening log eCRF must be completed for every subject who signs the ICF.

During the recruitment period, the distribution of UA, NSTEMI, and STEMI subjects will be monitored. If the percentage of STEMI subjects is projected to exceed 40% by the end of the recruitment period, then recruitment of STEMI subjects may be closed if deemed appropriate.

NOTE: The selection of individual medications, dosages, or titration schemes are left to the discretion of the investigator, although it is strongly recommended that treatments conform to current standard of care. In particular, all subjects should be on antiplatelet therapy (at minimum aspirin) and a statin, unless not indicated according to treatment guidelines or contraindicated in the opinion of the investigator. It should be noted that darapladib has no known effects on LDL-C or high-density lipoprotein cholesterol (HDL-C) levels. In regard to the intensity of statin therapy to achieve optimal LDL-C goals the investigators are referred to recent professional guidelines. In subjects with contraindications or intolerance to statins, the investigators are strongly encouraged to use alternative LDL-C lowering therapy. **See SOM for current treatment guidelines.**

Treatment Phase

The Treatment Phase begins at randomization.

Subjects who qualify for the study will be randomized 1:1 to once daily doses of oral Darapladib Enteric Coated Tablets, 160 mg or matching placebo (hereafter referred to as investigational product [IP]) and enter the Treatment Phase. **During the Treatment Phase, subjects will return for scheduled clinic visits at Month 1, Month 3, Month 6 and then every 6 months thereafter for the duration of the study. In addition, scheduled telephone visits will be conducted beginning at Month 9 and then every 6 months thereafter for the duration of the study. If a subject permanently discontinues treatment with IP prior to the end of the study, then the subject must be followed by telephone visits, in clinic, or other means until the end of the study unless consent is withdrawn.**

NOTE: 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.

During the study, **laboratory results of clinical concern** (e.g., LDL-C and HDL-C values) **will be provided to the investigators to intensify or modify pharmacological interventions in individual subjects. In addition, investigators will be provided with updates at regular intervals that summarize adherence to guideline mandated therapies** (e.g., blood pressure [BP], aspirin, P2Y12 inhibitors, statins, ACEi/angiotensin II receptor blockers [ARBs], and β-blockers) on the study level, country level, and the site level. **See SOM for current treatment guidelines.**

End of Treatment (EOT)

NOTE. The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed in clinic at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance).

End of Study (EOS)

When it is projected that approximately 1500 reports of first occurrence of MACE have occurred, the sponsor will notify investigators to begin scheduling end of study contacts for all their study subjects within a defined EOS period.

The EOS contact should be scheduled within the protocol-defined visit intervals (e.g., ± 20 days from the scheduled clinic visit) based on the original visit schedule, with the additional requirement that the visit/contact occurs within the pre-defined EOS period for

all subjects. In addition, survival status searches for subjects who are lost to follow-up or who withdrew consent for further participation in the study should be conducted during the EOS period where possible.

Every effort should be made to conduct the EOS contact in the clinic (i.e., face to face) during the EOS period for all subjects who are either on treatment, in post-IP phone/clinic follow-up, or in third party follow-up. Procedures for the EOS contact will be performed accordingly based upon whether the visit represents an EOT, Follow-up, or other visit as previously defined in the protocol (see [Table 2](#) and [Table 4](#)). If a subject refuses to return to clinic during the EOS period, then the visit should be conducted by telephone where appropriate. Refer to the Site Operations Manual for further details regarding scheduling of clinic EOS contacts.

Follow-up Phase

The Follow-up Phase begins the day after the final dose of IP.

At the end of the study, a Follow-up Visit will be scheduled to occur 35 ± 7 days after the final dose of IP. If all AEs and serious adverse events (SAEs) have resolved at the time of the Follow-up Visit, no further AE data (except for those events described in Section [6.4.6](#) and Section [6.4.9](#)) will be collected. In general, unless the investigator and sponsor discuss an alternative, ongoing AE and SAE data will be collected up to 35 days after the last dose of IP or until the Follow-up Visit, whichever is longer, after which no further data (except for those events described in Section [6.4.6](#) and Section [6.4.9](#)) will be collected. Before scheduling any additional clinic visits after the Follow-up Visit, the investigator should first discuss the situation with the sponsor.

The Follow-up visit may be conducted by telephone if the subject has completed an ‘in-clinic’ EOT/Early Withdrawal (EW) visit and has no unresolved or new safety concerns present at the EOT/EW visit (i.e., elevated liver function tests [LFTs], unresolved SAEs or other safety concerns that, in the investigator’s opinion, requires an in-clinic Follow-up visit).

Subjects with **unresolved or new safety concerns** present at the EOT/EW visit must have an ‘in-clinic’ Follow-up visit. For those subjects unable to participate in an ‘in-clinic’ Follow-up visit (i.e., documented subject refusal, subject hospitalized, etc.), the reason must be documented in the source documentation and a telephone Follow-up visit may be conducted.

NOTE: Subjects who permanently discontinue IP prior to the end of the study should have a Follow-up Visit scheduled to occur 35 ± 7 days after the final dose of IP, but will be followed for clinical outcomes until study termination, unless the subject withdraws consent for any further study-related contact. Additional information regarding survival status will be collected if it is available to the public. See Section 4.4, Stopping IP Early or Withdrawal from the Study, for more information.

3.2. Discussion of Design

Study Design

This study is a clinical outcomes study. The original primary clinical endpoint, MACE (defined as composite of CV death, non-fatal MI and non-fatal stroke), is a well-established endpoint for CV trials. The primary endpoint of the study was amended to major coronary events, defined as the composite of CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia, prior to unblinding the study data.

An external Independent Data Monitoring Committee (IDMC) will monitor safety in the study and an independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina and heart failure requiring hospitalization).¹ Therefore all components of major coronary events were also adjudicated by the CEC.

Because the study is powered on a predefined number of clinical events, the number of subjects required and study duration may vary from that stated in the protocol.

Dosing Regimen

Once daily oral doses of Darapladib Enteric Coated Tablets, 160 mg or matching placebo, **to be taken with food and swallowed whole (not chewed or crushed)**, will be added to standard of care in this study.

Dose Rationale

The goal of treatment with darapladib is to achieve near maximal inhibition of Lp-PLA₂ in the plaque with a resultant reduction in the risk of major coronary events, while maintaining an acceptable safety and tolerability profile. The 160 mg (enteric coat micronized free base tablet formulation) of darapladib has been chosen to progress into Phase III by linking together the pharmacokinetic (PK), pharmacodynamic (PD) and safety profiles of darapladib as seen in the range of Phase I and II studies summarized below. Refer to the Investigator's Brochure (see SOM for current version of the Investigator's Brochure) for further information on darapladib.

¹ **NOTE:** Details of the scope and criteria for clinical adjudication by the CEC are delineated in the separate charter of the CEC.

- **PK of different formulations of darapladib:** In the healthy volunteer study LPL101560, the PK and PD (i.e., plasma Lp-PLA₂ activity) profile of the enteric coat micronized free base tablet formulation 160 mg dose (i.e., formulation/dose to be used in this study) was similar to the 80 mg non-enteric coat free base formulation used in the early Phase I and II studies. Therefore, it is expected that similar biological effects are elicited using the 160 mg enteric coat formulation.
While enteric coating results in more variable time of maximal plasma concentration (Tmax) and reduced bioavailability, the terminal half-life for both formulations is approximately 126 hours which supports once-daily dosing (Study LPL112498).
- **Intra-plaque PD effects:** In subjects with carotid disease (Study 010), the 40 and 80 mg doses of the non-enteric coat formulation of darapladib were administered once daily over 14 days to patients undergoing elective carotid endarterectomy. A 52% (40 mg dose) and an 80% (80 mg dose, equivalent to 160 mg of enteric coat formulation) inhibition of Lp-PLA₂ activity (radiometric assay) was seen within carotid plaque removed during surgery [Johnson, 2004]. A post hoc analysis of the plaque provided evidence of a significant effect of the highest dose of darapladib on markers of apoptosis, caspase-3 and caspase-8, consistent with changes to a “less vulnerable” phenotype [Shi, 2007a].
- **Plasma PD effects:** In subjects with CHD or CHD risk-equivalent (Study LPL104884), the 160 mg enteric coat micronized free base tablet formulation of darapladib was administered to subjects who were also treated with atorvastatin 20 or 80 mg [Mohler, 2008]. This dose produced significant and sustained inhibition of Lp-PLA₂ activity after 12 weeks of dosing (88% by radiometric assay and 66% by colorimetric assay compared with placebo).² Sustained inhibition of plasma Lp-PLA₂ activity was seen over the 12 weeks of dosing and was independent of statin dosage. A significant reduction in the inflammatory biomarker interleukin-6 (IL-6) was also seen.
- **“Supratherapeutic” doses:** Darapladib enteric coat micronized free base tablets 160, 320 and 480 mg have been studied in healthy volunteers (Study LPL107988) to evaluate PK and PD of darapladib “supratherapeutic” doses. For a 3-fold increase in dose from 160 to 480 mg, there was a less than dose proportional increase in the mean darapladib area under the plasma concentration vs. time curve [AUC(0- τ)] and maximum drug concentration (Cmax) of only 2.5 fold and 2.8 fold respectively, following repeat dosing, with little additional inhibition of Lp-PLA₂ activity (from 87% to 92%, radiometric assay). Therefore, there seems no PD advantage of a further increase in the dosage of darapladib above 160 mg, but an increase in dose would mean a narrowing of the safety margin before the no-observed-adverse-event-level was reached.

² **NOTE:** Different assays of Lp-PLA₂ activity have been used during clinical development of darapladib. The radiometric assay was used in initial clinical studies, whereas the more practical colorimetric assay was introduced in larger clinical trials. Although these assays report numerically different inhibition of Lp-PLA₂ activity with darapladib administration, radiometric and colorimetric assays exhibit excellent inter-assay correlations (Pearson correlation coefficient is r=0.97, p<0.0001) [Mohler, 2008].

- **Imaging data:** A coronary IVUS Integrated Biomarker and Imaging Study (IBIS-2/Study 026) demonstrated that necrotic core expansion occurs in patients with chronic CHD or ACS receiving standard of care treatment for 1 year after initial evaluation (IVUS-virtual histology). Darapladib Enteric Coat Tablets, 160 mg (micronized free base formulation) halted this process, resulting in a significant difference with placebo [Serruys, 2008]. As the necrotic core is considered a key characteristic of high risk (vulnerable) plaques, darapladib treatment may represent a new therapeutic approach for CV risk reduction if the benefit of this intervention is confirmed by the results of event-driven outcomes trials.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 14,500 subjects with ACS are planned to be screened in order to randomize a minimum of approximately 11,500 total subjects, or at least 5750 subjects per treatment arm. It is planned that subject accrual will occur across a minimum of approximately 900 sites worldwide over a minimum period of approximately 24 months.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the IP that may impact subject eligibility is provided in the Investigators Brochure for darapladib (see SOM for current version of the Investigator's Brochure).

NOTE: Criteria that involve laboratory results may be based on local laboratory values obtained **≤ 8 weeks prior to randomization** (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during qualifying hospitalization). If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS.**

Subjects eligible for enrollment in the study must meet **all of the following criteria:**³

Signed written informed consent prior to beginning study-related procedures (subject must understand the aims, investigational procedures and possible consequences of the study).

³ **NOTE; 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.

Male or female aged at least 18 years, inclusive, at randomization. Female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy (refer to [Appendix 1](#)).⁴ 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. In Taiwan, subjects must be aged at least 20 years, inclusive, at randomization.

Hospitalization for ACS (unstable angina, non-ST segment elevation MI, or ST segment elevation MI) ≤30 days prior to randomization:

- a. **Unstable angina (UA)** is defined as ischemic chest discomfort (or equivalent) that occurs at rest with at least 1 episode lasting ≥10 minutes and is accompanied by new or presumably new ST segment deviation (transient [<20 minutes] elevation ≥0.1mV or dynamic horizontal/down-sloping depression ≥0.05mV) in at least 2 contiguous leads without diagnostic biochemical changes in cardiac enzymes (serum troponin I or T, or creatine kinase-MB).
- b. **Non-ST segment elevation MI (NSTEMI)** is defined as ischemic chest discomfort (or equivalent) that occurs at rest with at least 1 episode lasting ≥10 minutes and is accompanied by a diagnostic elevation in cardiac biomarkers of myocardial injury (serum troponin I or T, or creatine kinase-MB) above the upper limit of normal without persistent ST segment elevation.
- c. **ST segment elevation MI (STEMI)** is defined as prolonged symptoms of ischemic chest discomfort (or equivalent) at rest (with at least 1 episode lasting >20 min) and new or presumably new electrocardiographic changes (persistent ST segment elevation ≥0.1 mV in ≥2 contiguous precordial leads or ≥2 adjacent limb leads or new LBBB) that are accompanied by a diagnostic elevation in cardiac biomarkers (serum troponin I or T, creatine kinase or creatine kinase-MB) above the upper limit of normal.

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 prior to qualifying ACS event.
- c. diabetes mellitus requiring pharmacotherapy.
- d. significant renal dysfunction (defined as estimated glomerular filtration rate [eGFR] ≥30 and ≤59 mL/min per 1.73 m²).^{5,6}

⁴ Female subjects must be post-menopausal (i.e., >12 consecutive months without menses with appropriate clinical profile, e.g., age appropriate and in the absence of hormone replacement therapy that would suppress menses), or have a documented hysterectomy, bilateral oophorectomy or current tubal ligation, or using a highly effective method for avoidance of pregnancy (refer to [Appendix 1](#)).

⁵ The abbreviated Modification of Diet in Renal Disease (MDRD) equation [[Brosius III](#), 2006] will be used to calculate eGFR using serum creatinine concentration according to local guidelines [[Myers](#), 2006].

⁶ **Note:** Dye-induced nephropathy following cardiac catheterization or PCI during index hospitalization for ACS does not constitute chronic kidney disease.

- e. polyvascular disease manifested in this ACS population as coexistent clinically diagnosed arterial disease in at least 1 peripheral arterial territory, defined as:
 - cerebrovascular disease defined as carotid artery disease,⁷ or as prior ischemic stroke⁸ that occurred >3 months prior to randomization [see definition(s) below].

OR

 - peripheral arterial disease (PAD)⁹ [see definition(s) below].

The subject must be clinically stable for 24 hours prior to randomization (clinical stability is defined as the absence of chest pain, hemodynamic instability [e.g., hypotension, requirement for inotropic therapy], or significant arrhythmia [e.g., arrhythmia requiring treatment]).

For subjects in whom a PCI is planned as part of management for the qualifying ACS event, the subjects should undergo PCI prior to randomization whenever possible.

4.3. Exclusion Criteria

NOTE: Criteria that involve laboratory results may be based on local laboratory values obtained **≤ 8 weeks prior to randomization** (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during qualifying hospitalization). If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS.**

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

1. Clinical or laboratory manifestations of ACS (e.g., chest pain, ECG changes or increase in cardiac enzymes) that is not believed to be thrombotic in origin or is believed to be secondary to other apparent illness (e.g., sepsis, profound anemia, tachycardia, hypertensive emergency or decompensated heart failure).

⁷ Carotid disease is defined as unilateral or bilateral carotid stenosis >60% OR history of carotid surgery or stenting.

⁸ Prior ischemic stroke is defined as documented focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting >24 hours. It is strongly recommended that neuroimaging, such as computed tomography (CT) scan or magnetic resonance imaging (MRI) be performed to confirm diagnosis. In the absence of neuroimaging, additional functional deficit must be documented by abnormalities in the modified Rankin Score 1-4 [Banks, 2007]. See [Appendix 5](#).

⁹ PAD is documented by one of the following: current intermittent claudication with objective evidence of vascular origin (refer to the SOM for the list of acceptable diagnostic tests), history of peripheral arterial stenting or surgery (including amputation due to vascular causes), or ankle-brachial index <0.9 in at least one ankle.

2. Absence of obstructive coronary artery disease (i.e., at least one stenosis [$>50\%$] in a major vessel, major branch or bypass graft) based on angiography, if performed, between the time of presentation with ACS and randomization. (**NOTE:** If all stenoses are successfully treated by PCI, the patient is still eligible.)
3. Planned coronary artery bypass graft (CABG) surgery or CABG surgery performed following the qualifying event and prior to randomization.
4. Cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), unstable liver disease (defined by the presence of any of the following felt 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 evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase $>1.5 \times$ upper limit of normal [ULN]; or alanine aminotransferase (ALT) $>2.5 \times$ ULN) or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study.¹⁰
5. Severe renal impairment (e.g., patients with an eGFR¹¹ $<30 \text{ mL/min}/1.73 \text{ m}^2$ or receiving chronic dialysis) or history of nephrectomy or kidney transplant (regardless of renal function).
6. Current severe heart failure (New York Heart Association [NYHA] class III or IV).
7. Poorly controlled hypertension despite lifestyle modifications and pharmacotherapy.¹²
8. Any life-threatening condition with life expectancy <2 years, other than vascular disease, that might prevent the subject from completing the study.
9. Severe asthma that is poorly controlled on pharmacotherapy.
10. Positive pregnancy test (all female subjects of childbearing potential must have a urine or serum β -human chorionic gonadotropin [hCG] pregnancy test performed within 7 days prior to randomization) or is known to be pregnant or lactating.
11. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions (Refer to [Appendix 2](#)), or severe allergic responses.
12. Alcohol or drug abuse within the past 6 months. Current mental condition (psychiatric disorder, senility or dementia), which may affect study compliance or

¹⁰ **Note:** Chronic stable hepatitis B or C are considered an exclusion if there are elevated liver chemistries (elevated ALT, alkaline phosphatase or bilirubin as defined in exclusion criterion 4) or if the subject is receiving (or will receive) significant immunosuppressive agent(s) due to the risk of hepatitis B reactivation.

¹¹ The abbreviated MDRD equation [[Brosius III](#), 2006] will be used to calculate eGFR using serum creatinine concentration according to local guidelines [[Myers](#), 2006].

¹² Poorly controlled hypertension refers to either systolic BP $>160 \text{ mm Hg}$ or diastolic BP $>110 \text{ mm Hg}$ (BP should be measured according to protocol-specified conditions; a mean of 3 measurements is preferred but not mandated). Patients may enter the study if the adjustment to BP medications results in the improved control of hypertension at the Baseline Visit.

prevent understanding of the aims, investigational procedures or possible consequences of the study.

13. Current or planned chronic administration of strong oral or injectable cytochrome P-450 isoenzyme 3A4 (CYP3A4) inhibitors.¹³
14. Subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory prior to randomization. Those with Lp-PLA₂ activity ≤20.0 nmol/min/mL will be excluded from participation in the study.¹⁴
15. Previous exposure to darapladib (SB-480848).
16. Use of another investigational product within 30 days or 5 half-lives (whichever is the longer) preceding the first dose of darapladib or matching placebo.
17. Currently in a study of an investigational device.
18. Any other reason the investigator deems the subject to be unsuitable for the study.

4.4. Stopping IP Early or Withdrawal from the Study

Subjects have the right to stop taking IP before the end of the study or withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject may also be asked to stop IP at the investigator's discretion. **In the event that a subject permanently discontinues IP before the end of the study, the investigator should continue to follow the subject by telephone or in clinic to assess study endpoints including MACE (see Section 6.3). In addition investigator should continue to report SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (see Section 6.4.6). Events of cancer and gastrointestinal (GI) polyps/neoplasms should be reported until the end of the study (as described in Section 6.4.9)**

Subjects who wish to permanently discontinue IP prior to the end of the study but continue in the study will be asked to return for an Early Withdrawal Visit as soon as possible. They will be encouraged to continue taking IP until the day before this visit. If they do not wish to continue taking IP until the day before the Early Withdrawal Visit, or if they cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the

¹³ Note: Examples of strong CYP3A4 inhibitors include, but are not limited to the **antiretrovirals** atazanavir, indinavir, nelfinavir, ritonavir, saquinavir; the **macrolide/ketolide antibiotics** clarithromycin, telithromycin, troleandomycin; the **systemic antifungals** ketoconazole, itraconazole, posaconazole, voriconazole; and the **vasopressin receptor antagonist** conivaptan. Refer to the SOM for acceptable treatment alternatives. Of note, weaker CYP3A4 inhibitors are allowed, including verapamil, diltiazem, or amiodarone.

¹⁴ Subjects homozygous for the 279F variant have no circulating levels of Lp-PLA₂ and would not expect to benefit from Lp-PLA₂ lowering therapy. This allele is most common in those of Japanese, Chinese, and Korean ancestry [Stafforini, 2009].

Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance). **After the Follow-up Visit, telephone visits will be used in place of scheduled clinic visits to maintain contact with the subject until the end of the study. Note: All subjects will be asked to return to the clinic during the EOS period for a final study contact (see Section 3.1).** Assessments required for Telephone Visits may be performed in the clinic.

Data Collection for Subjects Who Decide to Stop Taking IP before the End of the Study (i.e., post-IP phone/clinic follow-up)

Every effort should be made to continue to follow subjects through the end of the study as these subjects will be included in the analyses of time to clinical events. Telephone visits or clinic visits should be used to follow subjects who permanently discontinue IP. These telephone calls or visits should be performed according to the original visit schedule. However, if the subject refuses regular follow-up by phone or in clinic, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable (see Table 4). If the subject declines all further contact with study personnel, subjects should be asked if they will allow follow-up for events through a family or friend contact, through their local physician or through medical records.

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication (See Section 6.4.6) as well as AEs/SAEs of cancer and GI polyps/neoplasms (See Section 6.4.9) should also be reported. **NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of the study.**

Data Collection Following Withdrawal of Consent for Further Participation in the Study

In subjects withdrawing consent to provide any additional information, no further study visits or study-related telephone contacts can be conducted. Additional information regarding survival status will be collected if it is available to the public.

For any subject who is found to be deceased following survival status searches, the death must be recorded on the death endpoint form and on the SAE-EP page. Wherever possible, cause of death should be provided if available in the public domain.

Any deaths reported through the survival status search must also be submitted as a study endpoint to be adjudicated by the Clinical Endpoint Committee. When submitting source information to the Clinical Endpoint Committee, investigators need to use their judgment to ensure only information available in the public domain is provided.

Prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, follow-up through a local physician or through medical records. Follow-up options will be summarized on a withdrawal of consent checklist that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study. The checklist needs to be completed for all randomized subjects who have withdrawn consent, even for those who withdrew prior to Amendment 3.

Possible Reasons for Discontinuation of Investigational Product

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

- Adverse experience requiring discontinuation including liver chemistry abnormalities (see Section 6.4.1)
- Subject becomes pregnant during the study
- Protocol deviation
- Decision by subject or proxy
- Sponsor terminated study treatment
- Lost to follow-up

Possible Reasons for Withdrawal from the Study

Possible reasons for subject withdrawal from the study include, but are not limited to, the following:

- Subject withdraws consent

5. STUDY TREATMENTS

5.1. Investigational Product and Reference Therapy

Darapladib Enteric Coat Tablets, 160 mg and matching placebo are supplied by GSK as white, round tablets with an enteric coating.

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 up to 30°C (86°F), protected from light and moisture, and in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the investigator and authorized site staff. IP must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

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 SOM for additional guidance).

Once daily oral doses of Darapladib Enteric Coat Tablets, 160 mg or matching placebo, **to be taken with food and swallowed whole (not chewed or crushed)**, will be added to standard of care in this study. Treatment will continue until it is projected that approximately 1500 reports of first occurrence of MACE have occurred.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule.

All subjects will be randomized before administration of any IP. Center-based randomization, using a randomization scheme generated by GSK, will be used. GSK's Registration and Medication Ordering System (RAMOS), an interactive voice response system (IVRS), will be employed to assign IP to the subjects. The investigator (or designee) must call into RAMOS to register all subjects once the ICF is signed.

Subjects who are eligible to participate in the double-blind Treatment Phase of the trial will be randomized to a treatment group through a call to RAMOS at the Baseline Visit. During this call, RAMOS will confirm the subject's electronic case report form (eCRF) number that was entered by the caller earlier during the same call, and provide the following additional sequences of numbers:

- A 6-digit randomization number which must be recorded in the subject's eCRF.
- 7-digit container number(s). Each container number corresponds to one bottle of 34 IP tablets to be dispensed to the subject from the investigator's inventory. Subjects will be instructed to finish the contents of one bottle before starting another. The total number of bottles dispensed to the subject will vary based on the visit schedule.

These numbers are unique to each subject and must not be re-assigned. The first dose of IP should be taken on the same day as randomization.

The RAMOS IVRS is a validated, Food and Drug Administration (FDA) 21 CFR11 compliant system which allows access to the treatment codes for packaging and supplies purposes. Access to the unblinded treatment codes are password restricted to packaging and supplies personnel with all personnel involved with the clinical conduct of the study remaining blinded 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 (darapladib 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, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.** Whenever possible, the investigator must first discuss options with the GSK Medical Monitor or the TIMI medical hotline **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK or the TIMI medical hotline as soon as possible, 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.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the blinded report may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Subjects should carry a card 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. Subjects must be made aware of the consequences of unblinding.

If the blind is broken **by the investigator**, the subject will be permanently discontinued from IP and all Early Withdrawal assessments will be completed. The subject will continue to be followed until the end of the study.

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 GSK IP dispensed and/or administered to study subjects, the amount 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

Assessments of compliance (i.e., adherence) will be completed at each post-randomization visit.

The number of IP tablets dispensed at each clinic visit will be recorded in the eCRF, and subjects will be instructed to return any unused IP at the next visit. All returned IP will be counted to determine the actual number of tablets taken by the subject and recorded in the eCRF.

Compliance at each visit will be determined as follows:

$$(\# \text{ dispensed} - \# \text{ returned}) \times 100 / (\# \text{ days since last visit})$$

Subjects estimated to have taken less than 80% or more than 120% of IP at two consecutive visits will be considered noncompliant. All attempts should be made to improve the subject's compliance in taking study medication if the subject is continuing in the study.

Investigators may temporarily suspend IP dosing at their discretion although the time off IP should be minimized. **If the total time off IP between visits is more than 1 month (or anticipated to be more than 1 month), it is recommended that the investigator contact the medical monitor or TIMI medical hotline.**

The purpose of this contact is:

- Awareness by the sponsor and TIMI of which subjects are requiring temporary IP suspension, for what reasons and for what duration.
- Provide opportunity if required for discussion and agreement of strategies and appropriateness of restarting IP, and/or of agreement when the subject should be considered permanently withdrawn from IP.

The exact dates of investigator-approved stopping and re-starting IP should be recorded in the eCRF. This investigator-initiated suspension of IP will not count toward overall compliance.

If IP is suspended >7 days in a woman of childbearing potential, a urine or serum pregnancy test must be performed prior to restarting IP.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

Medications and therapies not specifically prohibited by the study are allowed. All concomitant medications taken during the study will be recorded in the eCRF.

5.6.2. Prohibited Medications and Non-Drug Therapies

Except for IP administered for this study, **no investigational drugs or investigational devices** (e.g., locally unapproved stents) are permitted from study entry through completion of the Follow-up Visit or 35 days after administration of the final dose of IP, whichever is longer.

Chronic co-administration of strong oral or injectable CYP3A4 inhibitors with IP is prohibited in the study. Alternative therapies should be used whenever possible. However, if required, subjects may receive short-term (i.e., ≤14 days) administration of a strong CYP3A4 inhibitor. Examples of strong CYP3A4 inhibitors include, but are not limited to, those listed below.

- The following antiretrovirals: atazanavir, indinavir, nelfinavir, ritonavir, saquinavir
- The following macrolide/ketolide antibiotics: clarithromycin, telithromycin, troleandomycin
- The following antifungals: ketoconazole, itraconazole, posaconazole, voriconazole
- The vasopressin receptor antagonist conivaptan

Refer to the SOM for acceptable treatment alternatives. Of note, weaker CYP3A4 inhibitors are allowed, including verapamil, diltiazem, or amiodarone.

5.7. Treatment after the End of the Study

Subjects may 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.

5.8. Treatment of Investigational Product Overdose

An overdose will be defined as any dose over the stated maximum of each of the study treatments.

There is no specific antidote for an overdose of darapladib; however, the Lp-PLA₂ inhibition is reversible and plasma levels of Lp-PLA₂ activity should return to baseline within several days upon discontinuation of dosing. Supportive care should be provided as appropriate.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 1 Time and Events Table – Through Randomization

Procedures	Screening Phase (begins when written informed consent is obtained and ends at randomization)	Baseline Visit (\leq 30 days after presentation with ACS)
Written Informed Consent	X	
Subject Demography	X	
Medical History / Detailed CV history	X	
Inclusion/Exclusion Criteria ¹	X	
Concomitant Medications		X
Vital Signs	X	x (within 2 days prior to randomization)
Full Physical Examination ²		x (within 2 days prior to randomization)
Modified Rankin Scale		X
12-lead ECG		x (within 2 days prior to randomization)
Adverse Events		X
Pregnancy Test (urine or serum) ³	X	x
Randomization		X
Blinded Lp-PLA ₂ activity ⁴		X
Blinded/Stored Biomarkers of CV risk		X
Genetics		X
HBsAg and hepatitis C antibody		X
Clinical Laboratory Tests	X ⁵	X ⁶
Urinalysis ⁷		X
IVRS	X	X
Dispense IP		X
Short Messaging Service (SMS) reminder system		X

Table 1 Time and Events Table – Through Randomization (Continued)

1. All inclusion/exclusion assessments must be obtained prior to randomization.
2. At minimum: height, weight, neck circumference, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eyes, ears, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, lower and upper extremities exam, sleep questionnaire and smoking status.
3. Obtain from women of childbearing potential only. A negative urine or serum pregnancy test must be obtained \leq 7 days prior to randomization.
4. Subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory prior to randomization; if eligible for study entry, Lp-PLA₂ activity is not repeated at Baseline.
5. Refer to the inclusion/exclusion criteria (Section 4.2 and Section 4.3) for clinical laboratory test results required for study entry (eGFR, total bilirubin, alkaline phosphatase, ALT). Local laboratory values may be used if obtained \leq 8 weeks prior to randomization (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during qualifying hospitalization). If unavailable, then obtain written informed consent and send samples to the central laboratory or an accredited local laboratory.
6. Blood samples for clinical laboratory tests (central laboratory) obtained following a 9 hour fast (i.e., no caloric intake), whenever possible.
7. Dipsticks for blood and protein in the urine will be used. If the dipstick is positive for protein, a urine sample will be sent to the central lab for assessment of ACR.

Table 2 Time and Events Table – Post-Randomization – All Subjects

Procedures	Treatment Visits						End of Treatment /Early Withdrawal ³	Follow-up Visit ^{2,3}
	Clinic Visit (\pm # calendar days)			Telephone Visit (\pm # calendar days)	Clinic Visit (\pm # calendar days)		Clinic Visit	Clinic (or telephone ³) Visit
	Month 1 (± 7)	Month 3 (± 14)	Month 6 ¹ (± 20) PLUS every 12 months	Month 9 ¹ (± 14) PLUS every 6 months	Month 12 ¹ (± 20) PLUS every 12 months	Unscheduled Visit ²	1 day after final dose of IP	35 \pm 7 days after final dose of IP
Assessment of MACE	x	x	X	x	x	x	x	x
Concomitant Medications	x	x	X	x	x	x	x	x
Vital Signs	x	x	X		x	x	x	x
Full Physical Exam ⁴					x	(x)	x	(x)
Brief Physical Exam ⁵	x	x	X			(x)		(x)
Modified Rankin Scale	x	x	X		x	(x)	x	x
12-lead ECG	x				x	(x)	x	(x)
Adverse Events	x	x	X	x	x	x	x	x
Pregnancy Test ⁶	x	x	X		x	(x)	x	x
Lp-PLA ₂ activity	x ⁷	x ⁷	x ^{7,8}				x ⁷	
Blinded/Stored Biomarkers of CV risk	x		Month 6 only				x	
Clinical Laboratory Tests ⁹ (Central lab)		x	X		x	(x)	x	(x)
Urinalysis ¹⁰			X			(x)	x	(x)
Events of cancer and GI polyps/neoplasms ¹¹	x	x	X	x	x	x	x	x
Assess IP compliance	x	x	X	Query Compliance (tablet count not required)	x		x	
Dispense IP	x	x	X		x			
IVRS	x	x	X	x	x		x	x
SMS reminder system	x	x	X	x	x		x	x

Table 2 Time and Events Table – Post-Randomization – All Subjects (Continued)

1. Visits will continue at the specified intervals until the end of the study. The subject will be contacted by telephone between clinic visits to assess AEs, SAEs, MACE and other clinical outcomes, and informal compliance.
2. The assessments indicated within parentheses as (x) are performed as needed to follow unresolved findings of clinical concern or as indicated by the subject's clinical status.
3. The End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose. If the End-of-Treatment/Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis. All subjects are required to complete a Follow-up visit 35 ± 7 days after the final dose of IP. However, the Follow-up Visit may be conducted by telephone under certain circumstances as described in Section 3.1 of the protocol. NOTE: Only assessments required at BOTH the Follow-up visit AND a Telephone visit should be performed for a Telephone Follow-up visit. **Samples for Lp-PLA₂ activity and stored biomarkers are not collected at the Follow-up Visit and should not be obtained if the EOT/EW visit is performed more than 24 ± 2 hours after last dose of IP.**
4. At minimum: height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, and lower and upper extremities exam.
5. At minimum: weight, lung and heart sounds.
6. Urine or serum β-hCG pregnancy test obtained from women of childbearing potential only.
7. Obtain sample (preferably at trough whenever possible, i.e., 24 ± 2 hours after the previous IP dose and immediately prior to the current IP dose). The subject should return a medication card with the exact time of IP dose recorded on the 2 days prior to the visit. (NOTE: the subject does not receive an IP dose on the day of the End of Treatment/Early Withdrawal Visit).
8. Obtain at Month 6 and Month 18 only.
9. Blood samples for clinical laboratory tests obtained following a 9 hour fast (i.e., no caloric intake) whenever possible. HbA1c obtained only in those subjects with diabetes mellitus. Fasting plasma glucose will be obtained from all subjects, including those diagnosed with diabetes mellitus.
10. Dipsticks for blood and protein in the urine will be used. If the dipstick is positive for protein, a urine sample will be sent to the central laboratory for assessment of ACR.
11. See Section 6.4.9 for details regarding events of cancer and GI polyps/neoplasms.

Table 3 Time and Events Table - Additional Assessments for Subjects Enrolled in Substudies

Procedures	Visits (\pm # calendar days)						End of Treatment / Early Withdrawal	Follow-up Visit ²
	Screening	Baseline	Month 1 (± 7)	Month 3 (± 14)	Month 6 ¹ (± 20) PLUS every 12 months	Month 12 ¹ (± 20) PLUS every 12 months		
PK (trough) PLUS Lp-PLA ₂ Activity ³			X	x	x ⁴			
PK (serial samples) PLUS Lp-PLA ₂ Activity ⁵				x	x ⁶			

1. Visits will continue at the specified intervals until the end of the study.
2. The Follow-up Visit is scheduled to occur 35 ± 7 days after the final dose of investigational product (IP).
3. Obtain samples for PK and Lp-PLA₂ activity at trough (24 \pm 2 hours after the previous IP dose and immediately prior to the current IP dose). Note: Trough samples for Lp-PLA₂ activity specified in [Table 2](#) may be used.
4. Obtain at Month 6 and Month 18 only.
5. Obtain samples for PK and Lp-PLA₂ activity at trough (24 \pm 2 hours after the previous IP dose and immediately prior to the current IP dose) and at 1, 2, 3, 4, 6, 8, 24 hours after dosing IP. Note: Trough samples for Lp-PLA₂ activity specified in [Table 2](#) may be used.
6. Obtain at Month 18 only.

Table 4 Time and Events Table – Assessments for Subjects Who Permanently Discontinue IP Prior to the End of the Study (It is preferred that these assessments be conducted every 3 months. However, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable. See Section 4.4)

Procedures	Phone/Clinic Visit	EOS Clinic Visit ¹
Assessment of MACE and other study endpoints	x	x
SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication (see Section 6.4.6)	x	x
Events of cancer and GI polyps/neoplasms (see Section 6.4.9)	x	x
Vital Signs		x

1. Every effort should be made to conduct the last visit in the clinic during the EOS period (see Section 3.1). If subjects are unable to return to the clinic a phone contact is allowed.

6.1. Dietary Restrictions

Subjects should be instructed to refrain from consumption of >240 mL daily of grapefruit juice, which may inhibit CYP3A4.

6.2. Critical Baseline Assessments

Refer to [Table 1](#) for a list of assessments obtained 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 patients enrolled in the study (see SOM for current treatment guidelines).

6.2.1. Sleep Questionnaire

CV events have been directly associated with sleep apnea and overnight shift work, and inversely associated with habitual duration of sleep. To further investigate these associations, a paper copy of a questionnaire that assesses sleep habits and risk for sleep apnea (e.g., snoring, fatigue while awake, overnight shift work and average hours of sleep) will be given to subjects for completion at the Baseline Visit. Neck circumference, also directly associated with risk for sleep apnea, will be measured at the Baseline Visit. The sleep questionnaire responses and neck circumference measurements will be evaluated for the association of baseline sleep habits and risk for sleep apnea with the risk of future CV events and outcomes. Details of the analysis are described in the Reporting and Analysis Plan (RAP).

6.3. Efficacy

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina and heart failure requiring hospitalization).¹⁵ Therefore all components of major coronary events were also adjudicated by the CEC. In addition, the CEC will confirm the cause of death as CV or non-CV. CV death will be further defined as related to CHD when appropriate. When there is a disagreement between the CEC and the principal investigator, the CEC's decision will be considered final. The detailed descriptions of the endpoint definitions necessary for adjudication are contained within the CEC charter.

6.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to the first occurrence of any component of **the composite of major coronary events that includes CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia** in an ACS population treated with Darapladib Enteric Coated Tablets, 160 mg compared with placebo.

¹⁵ NOTE; Details of the scope and criteria for clinical adjudication by CEC are delineated in the separate charter of CEC.

6.3.1.1. Coronary Heart Disease Death

CHD death is defined as the occurrence of a fatal MI, death caused by documented cardiac arrest (e.g., ventricular fibrillation or other lethal arrhythmia without known secondary causes), death resulting from heart failure in a patient with known CHD, death from other forms of acute or chronic CHD, unwitnessed death of unknown origin or sudden death.

6.3.1.2. Myocardial Infarction

MI is defined according to the Universal Definition of MI [Thygesen, 2007].¹⁶ The information provided represents the guiding principles.

Acute MI: evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

- Detection of rise and/or fall of **cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of a normal reference population** (URL = upper reference limit) together with evidence of myocardial ischemia with at least one of the following (Note: The MI decision limit or ULN can be used if 99th percentile is unavailable):
 - Symptoms of ischemia;
 - Electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new LBBB; see [Appendix 3](#): ECG manifestations of acute myocardial ischemia [in absence of left ventricular hypertrophy (LVH) and LBBB] [Thygesen, 2007] for details);
 - Development of pathological Q waves in ECG;
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (pre-event imaging data required for verification of new abnormalities).
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but **death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.**
- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural necrosis. By convention, **increases of biomarkers greater than 3 x 99th URL have been designated as defining PCI-related myocardial infarction.** A subtype related to a documented stent thrombosis is recognized.

¹⁶ **NOTE:** The following definition applies to both fatal and non-fatal MI. Fatal MI will be counted as cardiovascular death. Non-fatal MI will be counted as a separate component of the MACE endpoint.

- For CABG surgery in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.
- **Pathological findings** of an acute MI.

Prior MI (i.e., diagnosed post-randomization): Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms (see [Appendix 4: ECG changes associated with prior myocardial infarction \[Thygesen, 2007\]](#) for details).
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause (pre-event imaging data required for verification of new abnormalities).
- Pathological findings of a healed or healing MI.

6.3.1.3. Urgent Coronary Revascularization for Myocardial Ischemia

Urgent coronary revascularization for myocardial ischemia is defined as ischemic discomfort at rest that prompts coronary revascularization (PCI or CABG) during the same hospitalization or resulting in hospital transfer for the purpose of coronary revascularization. PCI is defined as any attempt at revascularization even if not successful (e.g., angioplasty, atherectomy or stenting).

6.3.2. Secondary Efficacy Endpoints

- The composite measure of **MACE** that includes the first occurrence of CV death,¹⁷ non-fatal MI¹⁸ or non-fatal stroke¹⁹ in darapladib-treated subjects compared with

¹⁷ **Note:** CV death is defined as death due to documented CV cause. Causes of CV deaths include but are not limited to deaths resulting from stroke, arrhythmia, sudden death (witnessed or unwitnessed), MI, heart failure, pulmonary embolism, PAD or complications of a CV procedure. Additionally, deaths not clearly attributable to non-CV causes will be considered CV deaths.

¹⁸ **Note:** See definition of MI in Section 6.3.1.2.

¹⁹ **Note:** Stroke is defined as the presence of a new focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting >24 hours, or results in death (in <24 hours). It is strongly recommended that neuroimaging, such as computed tomography (CT) scan or magnetic resonance imaging (MRI), be performed to confirm diagnosis. In the absence of neuroimaging, additional functional deficit must be documented by a change in the modified Rankin Score [[Banks, 2007](#)]. If neurologic symptoms last <24 hours, new brain infarction has to be confirmed by diffusion-weighted MRI showing the presence of a new brain infarct. Alternate forms of neuroimaging will be accepted only if it can be demonstrated that a defect is new. In addition, location of a defect must be consistent with the observed neurological symptoms. Confirmed retinal arterial ischemic event (embolism,

placebo

- The **individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]) in darapladib-treated subjects as compared with placebo.
- **Individual components of major coronary events** (CHD death²⁰, MI [fatal and non-fatal], urgent coronary revascularization for myocardial ischemia²¹)
- The composite measure of **total coronary events** that include the first occurrence of CHD death, non-fatal MI, hospitalization for unstable angina,²² or any coronary revascularization procedure (excluding PCI planned prior to randomization but performed after randomization) in darapladib-treated subjects as compared with placebo.
- Any coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).
- The first occurrence of any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- The composite of CHD death and non-fatal MI
- All cause mortality.

6.3.3. Others

- Total incidence of first and subsequent coronary events comprising major coronary events.
- Total incidence of first and subsequent CV events comprising MACE.
- Heart failure requiring hospitalization.²³

infarction) will be considered a stroke. Stroke will be further classified as ischemic, hemorrhagic, ischemic with hemorrhagic conversion, or type uncertain.

²⁰ Note: See definition of CHD Death in Section 6.3.1.1

²¹ Note: See definition of urgent coronary revascularization for myocardial ischemia in Section 6.3.1.3

²² Note: Hospitalization for unstable angina is defined as one of the following but not fulfilling the criteria for MI: (a) ischemic discomfort at rest associated with ECG changes leading to hospitalization OR (b) ischemic discomfort at rest regardless of ECG changes leading to hospitalization AND revascularization during the same admission OR (c) ischemic discomfort at rest in hospital associated with ECG changes OR (d) ischemic discomfort at rest in hospital without ECG changes resulting in revascularization during the same admission. The event will not be considered unstable angina if, after invasive/non-invasive testing or other diagnostic testing, the discomfort is found not to be caused by myocardial ischemia. Details of ECG changes indicative of ischemia are described in the CEC charter and in the eCRF.

²³ Note: Heart failure requiring hospitalization is defined as admission to hospital or attendance at an acute healthcare facility for administration of intravenous diuretic treatment, escalation of diuretic doses, and/or inotropes. Confirmation of heart failure diagnosis is required by chest imaging demonstrating pulmonary congestion or edema [Held, 2007] OR, in patients *without* available chest imaging, at least one of the following: pulmonary edema (i.e. rales >1/3 up the lung fields thought to be of cardiac

- **Total vascular events** that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary [excluding PCI planned prior to randomization but performed after randomization]), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo. NOTE: Unplanned hospitalization for a new peripheral arterial ischemic event should be reported as the endpoint “Hospitalization for a non-coronary ischemic event”. This includes patients with acute limb or visceral ischemia, including acute ischemia caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure.
- **The composite of total coronary events** (CHD death, non-fatal MI, hospitalization for unstable angina, or any coronary revascularization procedure [excluding PCI planned prior to randomization but performed after randomization]) in darapladib-treated subjects compared with placebo, **excluding target lesion revascularization** (i.e., restenosis) in subjects treated with PCI prior to randomization.
- New onset diabetes mellitus (post-randomization diagnosis is based on investigator judgment).
- Chronic inhibition of plasma Lp-PLA₂ activity (see [Table 1](#), [Table 2](#), and [Table 3](#) for more information).
- Health care resources utilization (i.e. hospitalization and major procedures). See Section [6.5](#) for more information.

6.3.4. Exploratory endpoints (substudies)

- Exploratory analysis of CV risk biomarkers and genetic assessments (see [Table 1](#), [Table 2](#), Section [6.7](#), Section [6.8](#) and [Appendix 6](#) for more information)
- Estimation of PK parameters of darapladib (see [Table 3](#) and [Appendix 8](#)).

6.4. Safety

Refer to [Table 1](#), [Table 2](#), and [Table 3](#) for the timing of all study assessments. **An unscheduled clinic or telephone visit may occur at any time at the subject's request or if the investigator believes an unscheduled visit is clinically warranted.**

6.4.1. Liver chemistry stopping and follow-up criteria

Phase III-IV liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below:

causes), pulmonary capillary wedge pressure >18 mm Hg, or BNP >500 pg/ml (or NT-terminal prohormone BNP >2500 pg/ml) [[Maisel](#), 2001].

1. ALT \geq 3xULN and total bilirubin \geq 2xULN ($>35\%$ direct bilirubin) OR (ALT \geq 3xULN and INR >1.5 , if international normalized ratio [INR] measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: 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 \geq 8xULN.
3. ALT \geq 5xULN but <8 xULN persists for ≥ 2 weeks.
4. ALT \geq 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for ≥ 2 weeks.

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately withdraw investigational product.**
- Report the event to GSK or the TIMI medical hotline 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 \geq 3xULN and total bilirubin \geq 2xULN ($>35\%$ direct), termed ‘Hy’s Law’, OR (ALT \geq 3xULN and INR >1.5 , if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants) **must be reported as an SAE**.

NOTE: 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.
- Subject continues in the study (IP is permanently discontinued) after completion of the liver chemistry monitoring as described below.
- Do not restart investigational product unless approval is granted by GSK Medical Governance (details for restarting investigational product are described in Section [6.4.1.1](#) and [Appendix 10](#)).

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 or hepatology consultation is recommended.

- Monitor subjects twice weekly until liver chemistries (ALT, Aspartate Aminotransferase [AST], alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

NOTE: bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin $\geq 2 \times \text{ULN}$, then the event should still be reported as an SAE.

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** 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 $\geq 5 \times \text{ULN}$ and $< 8 \times \text{ULN}$ which exhibit decrease to ALT $\geq 3 \times \text{ULN}$, but $< 5 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$, without hepatitis symptoms or rash and who can be monitored weekly for 4 weeks:

- Can continue IP
- 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 or fewer of monitoring, ALT $< 3 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$, 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 immunoglobulin M (IgM) antibody;
 - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
 - Hepatitis C ribonucleic acid (RNA);
 - Cytomegalovirus IgM antibody;
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
 - Hepatitis E IgM antibody (if subject resides outside the United States of America [USA] or Canada, or has travelled outside USA or Canada in past 3 months);
- Blood sample for PK analysis, obtained within 72 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior

to blood sample draw in the eCRF. 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 SOM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin $\geq 2 \times \text{ULN}$.
- 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 $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ ($> 35\%$ direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease

6.4.1.1. Restarting Investigational Product

IP Restart Following Transient Resolving Liver Events Not Associated with Drug-induced (IP or non-IP) Liver Injury

Approval by GSK for IP restart can be considered where:

- The local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) has approved that **subjects at the site can be considered for restart of IP** as described in [Appendix 10](#).
- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to a) within the normal range OR b) $\leq 1.5 \times$ baseline and ALT $< 3 \times \text{ULN}$.
- GSK will inform the investigator of the decision to restart or not restart IP.
- If restart of IP is approved by GSK, the subject must provide signed informed consent specifically for the restart, which clearly describes risks and possible benefits of IP re-start. Documentation of informed consent must be recorded in the study chart.

- Subjects approved by GSK for restarting IP must return to the clinic within one month after IP re-start for repeat liver chemistries. If these are elevated but not meeting protocol-defined liver stopping criteria as per Section 6.4.1 of the protocol, they should be repeated monthly, or sooner in accordance with investigator judgment, until no longer elevated or increasing. If protocol defined stopping criteria for liver chemistry elevations are met after restarting IP, IP must be permanently stopped and/or subjects must be followed as per Section 6.4.1.

6.4.2. 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.

6.4.2.1. 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.

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 investigational product 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 IP or a concomitant medication (overdose per se will not be reported as an AE/SAE).
- “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 is 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.

- 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.
- Also see Section [6.4.4](#).

6.4.2.2. 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 out-patient setting. 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 judgement 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, 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.

6.4.3. 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.

All events of possible drug-induced liver injury with hyperbilirubinemia (defined as $\text{ALT} \geq 3 \times \text{ULN}$ **plus** total bilirubin $\geq 2 \times \text{ULN}$, or Hy's Law events, OR [$\text{ALT} \geq 3 \times \text{ULN}$ and $\text{INR} > 1.5$ **if not on anticoagulation therapy**]) require immediate study drug cessation and reporting as an SAE.

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 $\geq 2.0 \times \text{ULN}$, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations > 1.5 (if not on anticoagulation therapy) suggest severe liver injury.

6.4.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following events are considered cardiovascular efficacy endpoints for this study, which will not be reported by GSK as SAEs and will not be subject to expedited reporting to regulatory agencies regardless of the "expectedness" or "relatedness" of the event: These events, when occurring locally, should be reported to local ethics committees according to local guidelines.

- CV death (i.e., deaths resulting from stroke, arrhythmia, sudden death [witnessed or unwitnessed], MI, heart failure, pulmonary embolism, PAD, or complications of a CV procedure)
- Non-fatal MI
- Non-fatal stroke
- Coronary revascularization
- Hospitalization for UA
- Heart failure requiring hospitalization

Additionally, any laboratory or ECG abnormalities associated with the diagnosis of individual components of these cardiovascular efficacy endpoints will not be reported as an SAE.

6.4.5. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK or designee 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 investigational product, must be promptly reported to GSK or designee.

All subjects who become pregnant prior to the end of the Treatment Phase **must be immediately withdrawn from IP**. These subjects will continue to be followed for CV events through the end of the study.

6.4.6. 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.

Start of AE Collection

AEs will be collected from the start of IP.

Completion of AE Collection

AE collection will continue until 35 ± 7 days after the final dose of IP or the Follow-up Visit, whichever is longer.

SAE Collection

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study-related changes 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. All SAEs will be reported to GSK or designee within 24 hours, as indicated in Section 6.4.7.

Collection of Events of Cancer and GI Polyps/Neoplasms

Events of cancer and GI polyps/neoplasms will be reported as AEs or SAEs according to the cancer reporting period described in Section 6.4.9.

6.4.7. Prompt Reporting of Serious Adverse Events and Other Events to GSK or Designee

SAEs, anaphylaxis, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly to GSK or designee 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
Severe allergic reaction, suspected anaphylaxis or anaphylactoid event	24 hours	1. Anaphylaxis Diagnosis CRF. If meets anaphylaxis criteria, then 2. SAE data collection tool 3. Hypersensitivity Reaction Record	24 hours	Updated 1. Anaphylaxis Diagnosis CRF 2. SAE data collection tool 3. Hypersensitivity Reaction Record
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase III-IV				
ALT \geq 3xULN PLUS Bilirubin \geq 2xULN (and/or INR $>$ 1.5 if not on anticoagulation therapy)	24 hours ¹	SAE data collection tool and Liver Event CRF and liver imaging and/or biopsy CRFs if available	24 hours	Updated SAE data collection tool. Updated Liver Event CRF
ALT \geq 8xULN; ALT \geq 5xULN with hepatitis or rash or \geq 3xULN and <5xULN that persists \geq 4 weeks	24 hours ¹	Liver Event CRF	24 hours	Updated Liver Event CRF
ALT \geq 5xULN plus bilirubin <2xULN	24 hours ¹	Liver Event CRF does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks	24 hours	
ALT \geq 5xULN and bilirubin <2xULN that persists \geq 2 weeks	24 hours ¹	Liver event CRF	24 hours	Updated Liver Event CRF
ALT \geq 3xULN and <5xULN and bilirubin <2xULN	24 hours ¹	Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 2 weeks		

1. GSK or the TIMI medical hotline to be notified at onset of liver chemistry elevations to discuss subject safety.

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

6.4.7.1. Regulatory reporting requirements for SAEs

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

GSK or designee 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 or designee 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 or designee policy and are forwarded to investigators as necessary.

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 or designee will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.4.8. Other Safety Outcomes

ECG (12-lead): Documentation of the ECG (not just the interpretation) will be maintained in the subject's source document record.

Physical exam:

- A **full physical exam** will assess, at minimum, height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, and lower and upper extremities exam.
- A **brief physical exam** will assess, at minimum, weight, lung and heart sounds.

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

Vital Signs

Sitting BP and heart rate will be measured at each visit. **Sitting vital signs are taken prior to obtaining blood samples** according to American Heart Association (AHA) guidelines [Pickering, 2005]:

- The subject should be asked to remove all clothing that covers the location of cuff placement;

- The subject should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum);
- The subject should be allowed to relax at least 5 minutes before taking the first BP;
- BP should be checked in both arms at the first examination, except in clinical situations that prohibit measuring pressure in one of the arms. If there is a difference in pressure between arms, the arm with the higher pressure should be used. The same arm should be used to measure blood pressure at all subsequent visits.
- After determining which arm to use for BP measurement, a single sitting measurement will be taken and recorded for heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

If possible, all measurements should use the same cuff size and same equipment at each visit.

Modified Rankin Scale: The modified Rankin Scale assesses functional deficits following a stroke ([Appendix 5](#)). The modified Rankin scale will be performed in all subjects regardless of stroke history. If possible, the same person should assess the modified Rankin Scale for an individual subject at each visit for that subject.

Laboratory evaluations:

During screening, if local laboratory test results required for enrollment (refer to inclusion/exclusion criteria Section [4.2](#) and Section [4.3](#)) are not available, samples must be collected and sent to the central laboratory or an accredited local laboratory for assessment of all of the following: eGFR, total bilirubin, alkaline phosphatase and ALT.

NOTE: For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS. In addition, subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory prior to randomization; if eligible for study entry, Lp-PLA₂ activity is not repeated at Baseline.

At the Baseline Visit, blood will be collected for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (third generation enzyme immunoassay) and sent to the central laboratory for analysis.

Beginning with the Baseline Visit, blood will be collected at the times specified in [Table 1](#) and [Table 2](#) for analysis at the central laboratory for the following safety labs:

- **Clinical chemistry:** blood urea nitrogen, calcium, chloride, serum creatinine, eGFR,²⁴ potassium, sodium, bicarbonate, hemoglobin subtype A1c (HbA_{1c}),²⁵ glucose (fasting whenever possible)²⁶
- **Lipids** (fasting whenever possible):²⁷ total cholesterol, LDL-C (calculated), HDL-C, triglycerides, non-HDL cholesterol
- **Liver chemistry:** alkaline phosphatase, ALT, AST, total bilirubin, total protein, serum albumin
- **Hematology:** hematocrit, hemoglobin, platelet count, white blood cell count, neutrophil count

Urinalysis: Dipsticks provided by the central laboratory will be used to assess for the presence of blood and protein in the urine at the times specified in [Table 1](#) and [Table 2](#). If protein is positive on dipstick, a random spot urine sample will be sent to the central laboratory for analysis of albumin:creatinine ratio (ACR).

- **Urine pregnancy testing:** For women of childbearing potential, within 7 days prior to randomization and at every subsequent clinic visit, urine β-hCG (using dipsticks provided by the central laboratory) or serum β-hCG will be assessed by the central laboratory. A positive urine pregnancy test may be confirmed by sending a serum sample to the central laboratory for analysis of β-hCG.

6.4.9. Events of Cancer and GI Polyps/Neoplasms

Timing of Collection for Events of cancer and GI polyps/neoplasms

Collection of events of cancer and GI polyps/neoplasms will be extended to include the period off IP for subjects who have permanently discontinued IP. These events will be recorded from randomization until the end of the study.

Data collected

Reports of new cancer, recurrence of cancer, or progression of cancer will be recorded in all randomized subjects. Progression will be defined as spread to local lymph nodes or contiguous organs, as well as metastases. Benign GI polyps and all other benign GI neoplasms will also be recorded.

²⁴ The abbreviated MDRD equation [[Brosius III](#), 2006] will be used to calculate eGFR using serum creatinine concentration according to local guidelines [[Myers](#), 2006].

²⁵ HbA1c obtained only in those subjects with diabetes mellitus.

²⁶ Plasma glucose (fasting whenever possible) will be obtained from all subjects, including those diagnosed with diabetes mellitus.

²⁷ Fasting is defined as no caloric intake for at least 9 hours [[NCEP](#), 2002].

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will be recorded from randomization to the end of the study. NOTE: As per a country-specific amendment in France, subjects in France who are diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis) must immediately discontinue IP. In the event that a subject permanently discontinues IP, every effort should be made by the investigator to follow the subject to assess study endpoints including MACE (See Section 4.4. "Stopping IP Early or Withdrawal from the Study").

For "events of cancer and GI polyps/neoplasms" recorded prior to institution of Amendment #3, study sites should provide the same requested information as for new cancers, neoplasms or polyps.

Adjudication of GI events

All GI neoplasms (malignant and benign) and all GI polyps (malignant, benign, and non-neoplastic) will undergo adjudication. GI is defined as the entire tract from the esophagus to rectum as well as the liver, biliary system/gall bladder and pancreas. The neoplasms include primary GI neoplasms and neoplasms metastatic to the GI system. Anal cancers will also undergo CEC adjudication to ensure misclassification has not occurred. Details of the scope and criteria for clinical adjudication will be included in the CEC charter.

6.5. Health Economic Outcomes

Health economic outcomes will be assessed in this study including medical resource utilization and cost-effectiveness outcomes. In addition to MACE, the following data will be collected as part of clinical data collection to facilitate economic evaluation:

- All kinds of revascularization procedures and amputation (excluding PCI planned prior to randomization but performed after randomization)
- All hospitalizations with discharge diagnosis

The health economic endpoints include:

- Total treatment cost (without cost of study)
- Cost per vascular event avoided (see Section 6.3.3 for definition of "total vascular events")
- Cost per Life Years Saved (LYS)
- Cost per Quality-Adjusted Life Years (QALY) gained.

The health utility and cost for events of interest are required for a complete economic evaluation and will be gathered from other sources (i.e. literature, database, or country-specific studies).

6.6. Pharmacodynamics

Blood samples to assess Lp-PLA₂ activity will be obtained from all subjects at Baseline, and at Months 1, 3, 6, and 18 and End-of-Treatment (note that subjects are not dosed on the day of the End-of-Treatment Visit). Whenever possible, on-therapy samples should preferably be obtained at trough (24 ± 2 hours after the previous dose and immediately prior to the current dose). Lp-PLA₂ activity will be assessed for all Baseline samples and for a subset of post-Baseline samples. Because Lp-PLA₂ levels can unblind treatment, the values will not be provided to investigators or to other blinded members of the study team during the course of the study.

During the Treatment Phase, the exact time of dosing with IP on the day of the visit (with the exception of End-of-Treatment/Early Withdrawal), 1 day prior to the visit and 2 days prior to the visit will be recorded in the eCRF by having the subject return a medication card on which the subject records this information. The exact time of blood sample collection will also be recorded in the eCRF. The samples should be collected and stored as instructed in the central laboratory manual. Samples will be shipped to the central laboratory for the appropriate assay.

6.7. Biomarker(s)

Plasma and serum samples to assess biomarkers of CV risk (e.g., may include, but are not limited to high sensitivity troponin, high sensitivity C-reactive protein [hsCRP], IL-6, and brain natriuretic peptide [BNP]) and other circulating biomarkers associated with atherosclerosis, coagulation, or related disease progression will be obtained at the times specified in [Table 1](#) and [Table 2](#) and stored by GSK and/or TIMI or one of their appointed designees. Biomarker analyses are considered exploratory and can be conducted in all subjects or in a subset of subjects. Details will be provided in the separate analysis plan and its amendments.

6.8. Genetics

Information regarding genetic research is included in [Appendix 6](#). The IRB/ IEC and, where required, the applicable regulatory agency must approve deoxyribonucleic acid (DNA) collection for future genetic assessments. The approval(s) must be in writing and will clearly specify approval of the genetic assessments (i.e., approval of [Appendix 6](#)). In some cases, approval of the genetics 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 genetic assessments is being deferred and in most cases, the study, except for genetic assessments, can be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, genetic assessments will not be conducted. Genetic analyses are considered exploratory and can be conducted in all subjects or in a subset of subjects. Details will be provided in the separate analysis plan and its amendments.

Patients who provide consent will have a blood sample taken for analysis. Particular genes of interest and further information regarding the genetics research are described further in [Appendix 6](#): Genetics.

7. DATA MANAGEMENT

For this study subject data will be entered into eCRFs, transmitted electronically to GSK and designees, 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. AEs and concomitant medications terms will be coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. An appropriate medical dictionary that covers all approved drugs in the region 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

8.1. Hypotheses

The primary analysis will test the following hypotheses:

- Null hypothesis: Hazard ratio for major coronary events for darapladib relative to placebo is equal to one. This is equivalent to a reduction in risk equal to zero.
- Alternative hypothesis: Hazard ratio for major coronary events for darapladib relative to placebo is not equal to one (i.e., two-sided test). This is equivalent to a reduction in risk not equal to zero.

The study is designed to show superiority of treatment with darapladib relative to placebo (i.e., hazard ratio less than one, or equivalently, reduction in risk greater than zero) on top of a background of standard care.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

This event driven study is designed to have 90% power to detect a 15.5% reduction in risk of MACE event (hazard ratio=0.845) for subjects treated with darapladib compared to placebo on top of a background of standard care. Assuming a placebo event rate of approximately 7.5% for the first year and 3.5% per year thereafter, with an overall type I error rate (alpha level) of 5%, a total of 1500 MACE are required to achieve approximately 90% power. Components of MACE are expected to make up approximately 20% events from CV death, 60% events from non-fatal MI, and 20% events from non-fatal stroke. All subjects will be followed until the required total number of events occurs. **NOTE: Because the primary endpoint was changed after the required number of MACE events was achieved, sample size calculations were not changed to reflect the new primary endpoint of major coronary events.**

The sample size calculation accounts for two sources of subject withdrawal that are assumed to be uniformly distributed over the duration of the study. There is expected to be an annual rate of 1% of subjects not assessable due to loss to follow-up, who will be censored at the time of withdrawal. In addition, subjects may stop taking study medication, but will continue to be followed up for outcomes. The hazard ratio of 0.845 accounts for an 8% annual discontinuation from treatment and is based on a weighted average of an on-therapy hazard ratio of 0.83 and a post-therapy hazard ratio of 1.0.

The IDMC will review data periodically throughout the trial and has the ability to stop the trial for safety at any time. In addition, 2 interim looks will be performed to assess for efficacy and potentially futility. A flexible alpha-spending function will be applied to account for interim assessments made by the IDMC and the final alpha for the trial will be adjusted accordingly. A high threshold will be applied for the assessment of efficacy at an interim look, i.e., $p<0.0005$ at the first interim analysis and $p<0.001$ at the second interim analysis, preserving a minimum of $p=0.048$ (4.8% significance) for the final analysis. Full details will be defined in the Reporting and Analysis Plan (RAP).

Assuming a recruitment duration of 24 months and the event rates above, a sample of size 11,500 would result in a total study duration of approximately 4.1 years (encompassing a projected median follow-up duration of approximately 3 years assuming uniform enrollment). If the enrollment pattern is J-shaped as opposed to uniform, the study duration will be extended by approximately 3-6 months. Sample size was calculated using EAST 5.1.

Center-based randomization is planned, where central randomization using permuted blocks is stratified according to center.

8.2.2. Sample Size Sensitivity

This is an event driven study, with the number of required events (1500) driven by the assumed treatment effect. If the true underlying reduction in risk is lower or higher than the assumed 15.5%, the power resulting from an observed 1500 events is shown in [Table 5](#).

Table 5 Assumptions for Power Calculation

Reduction in Risk	Hazard Ratio	Power
11%	0.89	61%
12.5%	0.875	73%
14%	0.86	83%
15.5	0.845	90%
17%	0.83	95%
18.5%	0.815	98%
20%	0.80	99%

If the placebo event rate is lower or higher than the assumed first year rate of 7.5% and subsequent annual rate of 3.5%, the resulting study durations are shown in [Table 6](#) (assuming the sample size remained fixed).

Table 6 Sample Size Sensitivity for 90% Power and 15.5% Reduction in Risk

Placebo First Year Event Rate	Placebo Post First Year Event Rate	Study Duration (n=11,500)
8%	4%	3.7
7.5%	4%	3.8
7%	4%	3.9
8%	3.5%	3.9
7.5%	3.5%	4.1
7%	3.5%	4.2
8%	3%	4.2
7.5%	3%	4.4
7%	3%	4.6

8.2.3. Sample Size Re-calculation

The event rate will be monitored using data blinded with respect to treatment assignment. Should the observed event rate be lower than anticipated or discontinuation rates (i.e., withdrawal from study or discontinuation of IP) higher than expected, then the sponsor and the Steering Committee will review the value of sample size re-calculation and a potential increase in study size or in number of events based on blinded data reviews.

The maximum sample size will be capped at 15,000 randomized patients. Sample size re-calculation is most pragmatically implemented prior to completion of recruitment. Therefore, if recruitment has been closed out, the duration of the trial may be extended in order to achieve the target number of 1500 MACE.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The primary population for analysis of major coronary events and secondary time-to-event outcomes will be the Intent-to-Treat (ITT) Population, consisting of all randomized subjects.

The Safety Population, consisting of all randomized subjects who received at least one dose of IP, and analyzed as treated, will be used for safety data.

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

Consistent with the ITT principle, only events occurring post-randomization will be included in the analysis, regardless of whether the subject discontinued IP.

8.3.2. Treatment Comparisons

8.3.2.1. Primary Comparisons of Interest

The primary comparison of interest is the comparison of hazard rates of major coronary events for darapladib vs. placebo (i.e. the Hazard Ratio). The ITT population will be utilized for this comparison. The comparison will be made at a nominal 5% significance level, adjusting for analyses using a flexible alpha-spending approach.

8.3.2.2. Sensitivity Analyses

Further sensitivity analyses of the primary efficacy endpoint will also be performed to assess the robustness of the primary results.

- An analysis of only on-treatment major coronary events will be performed in the ITT population.
- An analysis of events as reported by the investigator (i.e., pre-adjudication) will also be performed.

All comparisons described above will use a Cox proportional hazards model to estimate the relative effect of darapladib versus placebo. The treatment effect will be assessed at a nominal 5% significance level, adjusting for interim analyses using a flexible alpha-spending function approach. Analysis results will be presented as hazard ratios, 95% confidence intervals and p-value.

In case data for some subjects is not available following loss to follow up, their event times will be treated as censored for statistical analyses. If the validity of the proportional hazards assumption is not acceptable, the treatment effect will be assessed using the Log-Rank Test and Kaplan-Meier Estimates.

8.3.3. Interim Analysis

The IDMC will review data periodically throughout the trial and has the ability to stop the trial for safety at any time. In addition, 2 interim looks will be performed to assess for efficacy and potentially futility. A flexible alpha-spending function will be applied to account for interim assessments made by the IDMC and the final alpha for the trial will be adjusted accordingly. A high threshold will be applied for the assessment of efficacy at an interim look, i.e., $p<0.0005$ at the first interim analysis and $p<0.001$ at the second interim analysis, preserving a minimum of $p=0.048$ (4.8% significance) for the final analysis. Full details will be defined in the reporting and analysis plan.

For the assessment of harm, a guideline of $p<0.01$ is proposed for the assessment of all-cause mortality, CV mortality and MACE. This flag would signal further examination of available data by the IDMC, with consideration of altering the conduct or terminating the study.

In the event of early stopping due to interim analysis results, subjects will be brought to the investigational sites for a final visit. The final analysis will include all data collected up to and including the final visit.

8.3.4. Essential Elements of the Analysis Plan

Any deviations from the original analysis planned in the protocol, which are agreed 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.

8.3.4.1. Efficacy Analyses

The primary efficacy outcome is major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia). Secondary outcomes include major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. The individual components of the primary composite endpoint and all cause mortality are all considered to be clinically meaningful and will therefore be analyzed separately; however, given the study design and underlying assumptions, these analyses will have less power and therefore are less likely to achieve statistical significance.

Multiplicity issues will be addressed in the RAP which will be finalized prior to breaking the study blind.

Statistical Models

A Cox proportional hazards regression model using SAS Proc PHREG will be used to assess the effect of treatment (p-value, hazard ratio point estimates and confidence intervals) on the primary endpoint; cumulative event rates will be calculated using the Kaplan-Meier method.

The proportional hazards assumption will be assessed, with details to be provided in the RAP. If the validity of the proportional hazards assumption is not acceptable, the treatment effect will be assessed using the Log-Rank Test and Kaplan-Meier Estimates.

For analysis of secondary time-to-event outcomes, cumulative event rates will be calculated using the Kaplan-Meier method, and hazard ratios will be calculated using a Cox proportional hazards model. If data for some subjects is not available following loss to follow up, their event times will be treated as censored at the last known participation date within the study.

Covariates and Subgroups of Interest

Analyses of efficacy will be performed for pre-specified subgroups to support the proposed indication. Sensitivity analyses will be conducted to assess the consistency of the overall effect within planned, clinically relevant subgroups of the overall population using a Cox proportional hazards regression, adjusting for the subgroup treatment and treatment by subgroup interaction. Given the study designs and underlying assumptions, analyses within subgroups will have less power and therefore are less likely to show statistical significance, especially when the size of the subgroup is small. Hazard ratio point estimates and confidence intervals will be estimated within subgroups, and p-values produced for the subgroup by treatment interaction.

Subgroups and covariates of specific clinical interest include diagnosis of ACS (UA, NSTEMI or STEMI), ethnic group, geographic region, gender, diabetes status, age, baseline BP, baseline eGFR, baseline LDL, baseline HDL and baseline Lp-PLA₂ activity levels. Additional subgroups will also be defined in the RAP that will be analyzed if there are sufficient numbers of subjects within each subgroup.

Primary and secondary outcomes will be analyzed to provide point estimates and confidence intervals for hazard ratios by region, along with p-value for region by treatment interaction.

Cumulative incidence curves by region will be produced to allow assessment of regional differences in event occurrence. Summary statistics on discontinuation of IP, loss to follow-up, concomitant therapy, BP and lipids will be produced by region to allow assessment of consistency across regions. Exploratory figures will be provided with a data point for each individual country to indicate how extreme the hazard ratio results are compared to the degree of expected variability, given the number of events observed in each country.

Integrated Summary of Efficacy

This trial is designed to assess ACS patients and is planned to be conducted in conjunction with a second mutually supportive outcomes trial of similar design in patients with chronic CHD. Upon completion, it is planned to combine the data from these two Phase III outcomes trials to inform on the overall clinical efficacy of darapladib for the following pre-specified outcomes including: MACE, individual components of MACE, major coronary events, total coronary events, all cause mortality, urgent coronary revascularization, and heart failure requiring hospitalization. The pooled analyses are expected to provide increased precision for estimating the magnitude of the treatment effects.

All comparisons described above will use a Cox-proportional hazards model to compare darapladib to placebo. Analysis results will be presented as hazard ratios, nominal 95% confidence intervals and p-values. Further details, including methods to address multiplicity, will be provided in a separate Integrated Analysis Plan which will be finalized prior to the unblinding of either study.

Biomarkers of Efficacy

Details regarding planned statistical analyses for biomarkers (other than Lp-PLA₂ activity) will be detailed in the RAP.

8.3.4.2. Safety Analyses

All AE data will be coded using the MedDRA dictionary and all medication terms will be coded using the GSK Drug Dictionary.

All safety evaluations will be based on the safety population. Clinical interpretation will be based upon review and displays of AEs, laboratory values and vital signs.

Extent of exposure

IP exposure will be summarized for the duration of exposure.

Vital signs and ECG

Values for each vital sign and ECG parameters will be summarized at each assessment by treatment group.

Details regarding planned statistical analyses for vital sign and ECG parameters will be provided in the RAP.

Safety laboratory values

Values for each safety laboratory parameter, and change from baseline in each parameter, will be summarized at each assessment by treatment group. A summary of the number, percentage, and rate per 1000 patient-years exposure for subjects who report at least one occurrence of laboratory values outside the normal range, and separately for those who report at least one occurrence of laboratory values of potential clinical concern, will be displayed by treatment group.

Adverse events

All AE data will be summarized, sorted by system organ class and preferred term for the safety population, consisting of all randomized subjects who received any investigational product, analyzed as treated.

Two-sided confidence intervals will be used to estimate the hazard ratio of commonly occurring adverse events with darapladib relative to placebo.

A summary of the number, percentage, and rate per 1000 patient-years of subjects who report at least one adverse event in the following categories will be displayed by treatment group:

- All AEs
- Drug-related AEs
- SAEs
- AEs leading to permanent discontinuation of IP/withdrawal from study

The hierarchical relationship between MedDRA system organ classes and preferred terms will be displayed for relevant adverse events.

Integrated Summary of Safety

This trial is designed to assess ACS patients and is planned to be conducted in conjunction with a second mutually supportive outcomes trial of similar design assessing the effects of darapladib in patients with chronic CHD.

Upon completion, it is planned to combine the data from this trial with other darapladib Phase III outcomes data in order to give greater precision for detecting any safety concerns (e.g., rates of unexpected SAEs, liver enzyme elevations, etc.).

Further details will be defined in a separate Integrated Analysis Plan which will be completed prior to the unblinding of either study.

8.3.4.3. Data Derivations***Discontinuation of IP***

Subjects who stop taking IP for whatever reason should continue to be followed for study outcomes and data will be reported up to the time of study conclusion. The primary analyses will include all post-randomization events irrespective of whether the patient discontinued study medication prior to the end of the study. A sensitivity analysis will also be performed assessing only events occurring while patients were on-therapy.

In case data for some subjects is not available following discontinuation of IP, their event times will be treated as censored for statistical analyses.

Derived and Transformed Data

For time to event endpoints (e.g., major coronary events), an event time (days) will be derived as the date the event occurred minus the date of randomization + 1 day. Censoring time will be calculated as the last recorded date in the eCRF minus the date of randomization + 1 day.

Change from baseline will be calculated as the post-baseline assessment value minus the baseline assessment value. If either value is missing then the change from baseline will also be missing. The distributional assumptions will be checked by graphical presentations of residuals and transformations used, if necessary. Further details will be specified in the RAP.

Methods of deriving and transforming data for any additional endpoints will be described in the RAP.

Assessment Windows

Full details of visit slotting and visit windows will be defined in the RAP.

Pooling of Study Sites

The study is planned to follow a center-based randomization, where central randomization using permuted blocks is stratified according to center. However, given the planned number of centers, the number of events per center will likely be too small to utilize individual centers for inclusion in the statistical model. Therefore, centers will be pooled into geographical regions (e.g. North America, Europe, Asia etc.) which will be assessed as a covariate in the sensitivity analyses. Pooling decisions will be made based on review of blinded data and will be described in the RAP.

8.3.4.4. Health Economic Outcomes Analyses

Individual components of “total vascular events” (see Section 6.3.3) will be compared between treatment groups.

Total LYS will be projected using clinical event data from the study in conjunction with epidemiology database and will be compared between treatment groups.

Total QALY gained will be calculated using health utility data for clinical events (i.e., “total vascular events” and SAEs) and compared between treatment groups.

Total treatment cost will be calculated for specific countries using clinical event data and resources utilization data from the study and local cost data for those events. The total treatment cost will be compared between treatment groups. These analyses will be performed on an “as needed,” country-specific basis and will not be included in the clinical study report.

Details of the health economic analyses, including specific regional analyses will be defined in the RAP.

8.3.4.5. Pharmacodynamic Analyses

Details regarding planned statistical analyses for Lp-PLA₂ activity will be provided in the RAP.

8.3.4.6. Genetic Analyses

Details of the analysis of genetic data will be specified in a Genetic Analysis Plan prior to conduct of any analysis. For additional information on the plans with respect to genetic data, see [Appendix 6](#).

9. STUDY CONDUCT CONSIDERATIONS**9.1. Regulatory and Ethical Considerations, Including the Informed Consent Process**

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US IND.

The study will be conducted in accordance with all applicable regulatory requirements, including a US IND.

The study will be conducted in accordance with Good Clinical Practice (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 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 must be obtained from each subject prior to participation in the study.

9.1.1. Short Messaging Service Reminder System

To help with the retention of the subjects and planning of their scheduled follow up throughout the study, subjects will be sent text messages via their mobile telephone, or e-mail reminders, regarding their scheduled appointments. Sites will gain consent from the subject via a separate ICF before enrolling their mobile phone number or e-mail address into the secure short messaging service (SMS) reminder system. The system will then transmit text messages or e-mails to the subject in the local language regarding their next appointment.

Subject participation in the SMS reminder system is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled. The SMS reminder system may not be available for all study sites or countries. Even if available, study sites or countries may choose not to participate in the SMS reminder system. All text message/e-mail content will be reviewed and approved by the IRB/IEC prior to use.

9.2. 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.

9.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance 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 audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

9.4. Study and Site Closure

When it is projected that approximately 1500 reports of first occurrence of MACE have occurred, the investigators will be notified to contact all subjects to schedule an End-of-Treatment visit to take place as soon as possible. The study SMS reminder system may be used to notify all subjects to return for their End-of-Treatment visit.

Upon completion or termination of the study, the 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 noncompliance. 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 or designee will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK or designee 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.

9.5. 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.

9.6. Provision of Study Results and Information to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The 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.

Upon completion of the clinical study report, GSK will ensure public disclosure of the clinical trial research results via the GSK Clinical Trials Register according to the GSK SOP and provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

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

GSK and TIMI intend to publish the results in the searchable, peer-reviewed scientific literature.

9.7. Steering Committee

The Steering Committee is the primary external advisory group for the study sponsor (GSK). The Steering Committee provides academic leadership, ensures proper study conduct and conformance to the protocol, advises and recommends changes to the protocol based on emerging scientific and/or clinical advances, advises on the selection of study sites, communicates with the media and external audiences when appropriate, and works with the sponsor to assist in patient identification strategies. Additional information about the Steering Committee is included in the Steering Committee charter, which is available upon request.

9.8. Clinical Endpoint Committee

An independent CEC will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for UA, and heart failure requiring hospitalization). Therefore all components of major coronary events were also adjudicated by the CEC. The CEC will also adjudicate all reported cases of polyps or neoplasms that involve the GI tract (entire tract from the esophagus to rectum as well as the liver, biliary system/gall bladder and pancreas) as described in Section 6.4.9. In addition, anal cancers will undergo CEC adjudication to ensure misclassification has not occurred. Procedures for adjudicating events are described in the CEC charter, which is available upon request.

9.9. 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.

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11. APPENDICES

11.1. Appendix 1: Highly Effective Methods For Avoidance Of Pregnancy In Women Of Childbearing Potential

The following is a list of highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year).

- Abstinence [[Hatcher](#), 2004]
- Oral Contraceptive, either combined or progestogen alone [[Hatcher](#), 2004]
- Injectable progestogen [[Hatcher](#), 2004]
- Implants of levonorgestrel [[Hatcher](#), 2004]
- Estrogenic vaginal ring [[Hatcher](#), 2004]
- Percutaneous contraceptive patches [[Hatcher](#), 2004]
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the SOP effectiveness criteria as stated in the product label [[Hatcher](#), 2004]
- 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](#), 2004]. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

Nooxynol-9 is the critical component in most spermicides, and is regarded as an acceptable spermicidal agent. Concern has been raised that nooxynol-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 [[WHO](#), 2003].

References

Hatcher RA, Trussell J, Stewart F, Nelson AL, Cates W, Guest F, Kowal DD, editors. Contraceptive Technology. New York: Ardent Media, 2004: 226. Table 9-2, "% of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year. United States", column entitled, "% of Women Experiencing an Unintended Pregnancy Within the First Year of Use. Perfect Use".

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**11.2. Appendix 2: Clinical criteria for diagnosing anaphylaxis
[Sampson, 2006]**

Anaphylaxis is highly likely when any **one** of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

- a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
 3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
 - a. Infants and children: low SBP (age specific) or >30% decrease in SBP. Note: Low SBP for children is defined as <70 mm Hg from 1 month to 1 year, <(70 mm Hg + [2 X age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.
 - b. Adults: SBP of <90 mm Hg or >30% decrease from that person's baseline

11.3. Appendix 3: ECG manifestations of acute myocardial ischemia (in absence of LVH and LBBB) [Thygesen, 2007]**ST elevation**

New ST elevation at the J-point in two contiguous leads with the cut-off points:

- ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2 and V3

AND/OR

- ≥ 0.1 mV in other leads

ST depression and T-wave changes

- New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads;

AND/OR

- T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

11.4. Appendix 4: ECG changes associated with prior myocardial infarction [Thygesen, 2007]

- Any Q-wave in leads V2 and V3 ≥ 0.02 s **OR** QS complex in leads V2 and V3
- Q-wave ≥ 0.03 s and ≥ 0.1 mV deep **OR** QS complex in leads I, II, aVL, aVF, or V4 through V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4 through V6; II, III, and aVF)^a
- R-wave ≥ 0.04 s in V1 and V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

^aThe same criteria are used for supplemental leads V7 through V9, and for the Cabrera frontal plane lead grouping.

11.5. Appendix 5: Modified Rankin Scale [Banks, 2007]

Grade	
0	No symptoms at all
1	No significant disability: despite symptoms, able to carry out all usual duties and activities
2	Slight disability: unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Death

11.6. Appendix 6: Genetics

Background

The study of variability in drug response due to hereditary factors in different populations is known as pharmacogenetics (PGx). There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (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). The contribution of genetically defined disease subtypes may influence variability in drug response and hence influence the outcomes of a clinical study. Thus, the application of exploratory genetics research may improve understanding of the influence of disease subtype on clinical study outcomes and provide a better understanding of disease that could be applied to define future clinical study design.

Some reported examples of PGx analysis include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	HLA (human leukocyte antigen)	Caucasian males with HLA B57 variant were at increased risk for experiencing hypersensitivity to abacavir
Tranilast	Restenosis prevention following coronary bypass [Roses, 2002]	UGT1A1	Drug induced hyperbilirubinemia explained by high proportion of affected patients having 7/7 TA repeat genotype, consistent with clinically benign Gilbert's Syndrome
Atorvastatin	Risk of MI and Response to High Dose Atorvastatin [Iakoubova, 2008]	KIF6	Carriers of 719Arg have a higher risk of myocardial infarction as well as benefit from high dose atorvastatin
Simvastatin	Hypercholesterolemia [Link, 2008]	SLCO1B1	Carriers of variant allele at increased risk of myopathy
Clopidogrel	Acute coronary syndromes [Mega, 2009]	CYP2C19	Among persons treated with clopidogrel, carriers of a reduced function CYP2C19 allele have lower levels of active drug metabolite, less platelet inhibition, and a greater risk of CV death, MI, or stroke.

Genetic Research Objectives

The objective of the exploratory genetics research is to investigate association between genetics variants and both outcomes and handling or response to darapladib. Specifically, we will investigate:

- Relationship between genetic variants and the PK and/or PD of darapladib or related drugs

- Relationship between genetic variants and safety and/or tolerability of darapladib or related drugs
- Relationship between genetic variants or genetically defined disease subtypes to clinical efficacy of darapladib and clinical study 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 genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no 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 whole blood sample (~6 mL) will be collected for the genetic research using a tube containing EDTA. The genetic sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. **Coded samples do not carry personal identifiers (such as name or social security number).** The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. 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, but may be taken at any time while the subject is participating in the clinical study.

Aliquots of the sample will be stored securely with GSK and the TIMI Study Group and may be kept for up to 20 years after the last subject completes the study. 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 study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then 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.

Genetic Analyses

Generally two approaches will be utilized to explore genetic variation in drug response.

1. 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.

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

- A single-nucleotide polymorphism (SNP) G994T (Val-to-Phe substitution of the mature protein, Val279Phe) of Lp-PLA₂. Lp-PLA₂ activity is decreased by half in heterozygous status while no activity has been reported in homozygous subjects [Stafforini, 1996; Satoh, 1999]. Other SNPs within Lp-PLA₂ that could be associated with LpPLA₂ activity may be investigated as well. A table of the SNPs of interest is attached below.

Position	rs Number	Allele
Promoter	rs13210554	C/T
Promoter	rs1421378	A/G
Intron 1	rs6935460	A/G
Arg92His	rs1805017	G/A
Ile198Thr	rs1805018	T/C
Val279Phe	rs16874954	G/T
Ala379Val	rs1051931	G/A

- 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 [Kathiresan, 2008] these SNPs are likely to 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 worse pharmacologic and clinical response to clopidogrel [Mega, 2009; Simon, 2009; Collet, 2009].

- The GSK Absorption, Distribution, Metabolism and Excretion (ADME) panel. Absorption, distribution, metabolism and excretion (ADME) genes play a central role in drug pharmacokinetics and pharmacodynamics (PK-PD). The GSK ADME panel contains genetic markers from one hundred and thirty-four enzymes, transporters and other genes involved in drug absorption, distribution, metabolism and excretion. The ADME panel may be used to investigate the relationship between genetic variants on the panel and pharmacokinetics, safety and efficacy of darapladib.

In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to darapladib. The genes that code for these proteins may also be studied.

2. 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.

Typically the methods used to identify markers that are associated with drug response are:

Hardy-Weinberg Equilibrium Testing

The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing.

Comparison of Demographic and Baseline Characteristics by Genotype

Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

Evaluation of Genotypic Effects

Analyses may be carried out to evaluate the degree of association between subject genotype (or haplotype) and selected parameters (e.g., pharmacokinetics, pharmacodynamics, clinical outcomes, treatment efficacy and safety). Where such genotypic tests are inappropriate (for example, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

Evaluation of Treatment by Genotype and Gene-Gene Interaction

In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele)

interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

Linkage Disequilibrium

For pairs of polymorphisms, the degree to which alleles from the two sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at two polymorphic sites within a gene are shown to be statistically associated with a response to investigational product, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the two sites are exerting independent effects.

Multiple Comparisons and Multiplicity

An adjustment to observed p-values may be made to limit erroneous conclusions due to multiple tests when multiple markers are evaluated (especially in the case of a genome scan for association).

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

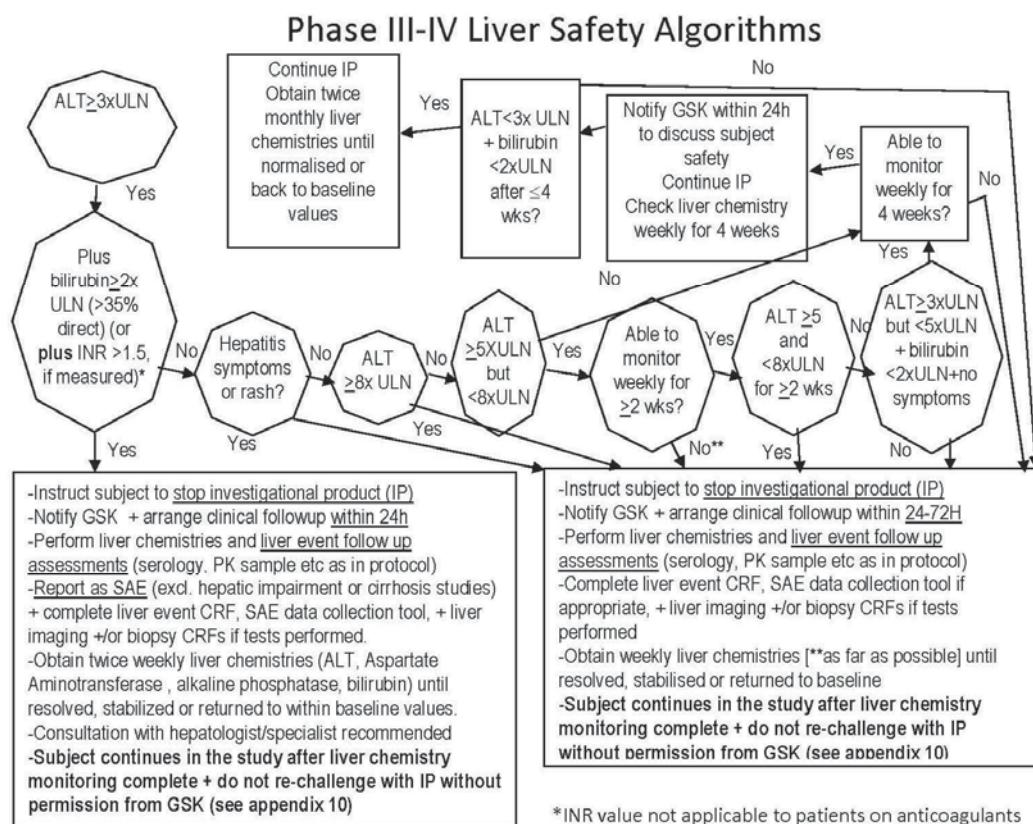
GSK may summarize the cumulative PGx research results in the clinical study report.

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.

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11.7. Appendix 7: Liver Chemistry Stopping and Follow-up Criteria



11.8. Appendix 8: Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Substudies

INTRODUCTION AND RATIONALE

Population PK is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest [Aarons, 1991]. Certain patient demographical, physiological, and therapeutic features, such as body weight, excretory and metabolic functions, and the presence of other therapies, may alter dose-concentration relationships. Population PK seeks to identify the measurable physiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dose can be appropriately modified.

It is currently planned in the Phase III program that approximately 5 to 7% of the total number of patients will contribute to the characterization of the PK of darapladib and the PK/PD relationship between plasma concentration and Lp-PLA₂ activity in the target patient population.

Pharmacokinetics of Enteric-Coated Formulation

The enteric coat micronized free base tablet formulation of darapladib will be used in the Phase III trials. This formulation has been used in a number of Phase I studies as well as the Phase IIB trials. PK results from the Phase I studies can be found in the Investigator's Brochure (See SOM for current version of the Investigator's Brochure). Results of the population PK analysis of the Phase IIB dose ranging trial are discussed briefly below.

Population Pharmacokinetics of Enteric Coated Formulation

A population PK model was developed to characterize the PK of darapladib following 12 weeks repeat dosing of 40, 80 and 160 mg enteric coat micronized free base tablet formulation in 690 patients with stable CHD or CHD-risk equivalent (Phase IIB Study LPL104884). Due to the sparseness of the plasma concentration-time data from the Phase IIB study, the structural model was initially developed using full concentration-time profiles obtained in healthy volunteers (n=41). Once the structural model was established, data from the Phase IIB patients were combined with the healthy volunteer data to develop the final population PK model.

The population PK model that best described the plasma concentration-time data for darapladib was a two-compartment model parameterized in terms of oral clearance (CL/F), apparent central (V₁/F) and peripheral (V₂/F) distribution volumes, and distributional clearance (Q/F). Consistent with Phase I data that showed less than dose-proportional increases in exposure for the enteric coat micronized free base formulation, different bioavailability terms (F) for the 80 mg dose and for doses \geq 160 mg (versus the 40 mg dose level) were included in the model. Additionally, separate estimates of CL/F

were determined for the Phase I and IIB data with patients exhibiting approximately 30% lower clearance.

The effects of patient covariates (age, weight, gender, race, atorvastatin dose, and CYP3A4 inhibitor co-medication) were assessed in population PK analysis using the combined data. In patients, both age and CYP3A4 inhibitor co-medication were shown to significantly influence oral clearance of darapladib. Based on the final population PK model, the oral clearance of darapladib decreases approximately 1% per year in patients older than 64 years and increases 1% per year in patients less than 64 years (e.g., a 74 year old patient will have an oral clearance 10% lower than those that are at the median age (i.e., 64) of the population participated in the Phase IIB study LPL104884).

Additionally, darapladib is primarily metabolized by CYP3A4 and potent inhibitors of this enzyme were prohibited in the Phase IIB study. However, a number of patients received weak or moderate inhibitors of CYP3A4 (including amiodarone, diltiazem, verapamil, cimetidine, fluoxetine, erythromycin, nefazodone, fluvoxamine, and sertraline) and CYP3A4 inhibitor co-medication was shown to decrease oral clearance by approximately 20%. The magnitude of the changes in oral clearance due to age or concomitant administration of CYP3A4 inhibitors is small considering the inter-subject variability in CL/F (approximately 38%) and therefore, the effects of these covariates are unlikely to be of any clinical significance.

Population Pharmacokinetics/Pharmacodynamics

The relationship between plasma darapladib concentrations and plasma Lp-PLA₂ activity has been described separately in both healthy volunteers (LPL101560) and in patients with stable CHD or CHD-risk equivalent (LPL104884) using population PK/PD modelling. The PK/PD relationship was best described by a direct-effect inhibitory sigmoidal Emax relationship. The plasma darapladib concentration that was estimated to cause 50% inhibition of plasma Lp-PLA₂ activity (IC_{50}) was similar between healthy volunteers ($IC_{50} = 4.19$ ng/mL) and patients ($IC_{50} = 6.76$ ng/mL) despite the fact that different activity assays were used (radiometric assay used in study LPL101560 and colorimetric assay method used in study LPL104884).

As part of the population PK/PD analysis conducted using the LPL104884 data, various patient covariates (i.e., age, weight, gender, race and atorvastatin dose) were explored. Based on preliminary population PK/PD modelling, gender and atorvastatin dose were found to statistically significantly influence baseline Lp-PLA₂ activity levels. Compared to male patients, baseline Lp-PLA₂ activity levels were approximately 11% lower in females while patients receiving atorvastatin 80 mg showed approximately 10% lower baseline levels compared patients receiving atorvastatin 20 mg. These findings are consistent with results from the statistical analysis of baseline Lp-PLA₂ activity data from the LPL104884 study. In addition, although the effect of age on IC_{50} for plasma Lp-PLA₂ inhibition was found to be statistically significant, the magnitude of the decrease in the IC_{50} with age was negligible and therefore, was not included in the final population PK/PD model.

Population PK and PK/PD Aspects of the Phase III Program

It is currently planned in the Phase III program that a subset (approximately 5 to 7%) of the total number of patients will contribute to the characterization of the PK of darapladib and the PK/PD aspects in the target patient population. Two separate sampling strategies are planned: serial PK sampling and trough PK sampling.

Serial PK sampling

Serial plasma PK samples (8 time points) over a 24-hour period will be obtained on two separate visits from approximately 75 patients receiving darapladib and 75 patients receiving placebo (approximately 150 patients in total). Patients must contribute to serial PK sampling on both visits to be considered evaluable. The objective of this sampling schedule is to collect full concentration-time profiles in order to adequately characterize the absorption profile of darapladib. It is planned to use these data to develop a population PK model in the target patient population and account for both inter-individual and inter-occasion variability in darapladib PK. These data will also be used to assess the influence of covariates (e.g., age, gender, weight) on the population PK parameters of darapladib and their associated variability. The limitation of this approach is the sample size of the subset of patients who participate in the full sampling design. Hence, only the impact of the most significant covariates may be evident.

Various sampling schemes have been evaluated to ensure that the data will result in reasonably precise estimates of AUC and Cmax while also taking into account feasibility for the study sites as well as inconvenience to patients (e.g., avoiding the need for an overnight stay). After establishing an appropriate sampling scheme, simulations were performed to evaluate whether this sampling scheme along with the planned number of patients combined from the two Phase III studies will be sufficient to detect the effect of potential covariates on the AUC of darapladib. The details of this analysis are briefly described in the Data Analysis Plan (DAP).

Trough PK sampling

Trough samples (on 4 visits) will be obtained from approximately 400 to 500 patients receiving darapladib and 400 to 500 patients receiving placebo (approximately 800 to 1000 patients in total).

The objective of this sampling schedule is to obtain trough data in a significant number of patients on four occasions. These data can then be used to define the inter-subject and inter-occasion variability in trough concentrations. Additionally, the data can be used to explore the relationship between trough exposure and patient covariates. In contrast to the population PK parameters estimated using the full concentration-time profiles, it is anticipated that the trough data will be more variable; however, the advantage is that a larger number of patients will be studied. Simulations have been performed to evaluate if the planned number of patients will be sufficient to detect the effect of potential covariates on trough concentrations of darapladib (see DAP for details).

For both sampling schemes, the exact time of sample collection will be recorded in the eCRF. The exact time of dosing on the day of the visit, 1 day prior to the visit and 2 days

prior to the visit will be recorded in the eCRF by having the subject return a medication card on which the subject records this information.

OBJECTIVES

Primary

Establish a population PK model adequate to describe the time-course and variability of plasma darapladib concentrations following repeat dose administration of Darapladib Enteric Coat Tablets, 160 mg in patients with ACS.

Secondary

Establish a population PK/PD model adequate to describe the relationship between plasma darapladib concentration and plasma Lp-PLA₂ activity following repeat dosing of Darapladib Enteric Coat Tablets, 160 mg in patients with ACS.

STUDY DESIGN

These PK/PD substudies are multicenter substudies of darapladib Study SB-480848/033 (the parent study). Centers participating in the parent study will be invited to participate in the PK/PD substudies. Subjects who qualify for the parent study are eligible.

Study Assessments

Sample Collection

Blood samples (approximately 3 mL) for darapladib PK analysis and blood samples (approximately 2 mL) for Lp-PLA₂ activity analysis will be collected into purple-top (EDTA) tubes at the following time points, relative to dosing:

(1) Serial Samples PK substudy

Month 3 and Month 18

Trough (24 ± 2 hours after the previous dose and immediately prior to the current dose)

1, 2, 3, 4 hours (± 15 minutes) after the current dose

6, 8 and 24 hours (± 30 minutes) after the current dose

It is important to note that, although small deviations from the planned sampling time is allowed as detailed above, every effort should be made to adhere precisely to the planned sampling schedule.

(2) Trough Sample PK substudy

Months 1, 3, 6 and 18

trough (24 ± 2 hours after the previous dose and immediately prior to the current dose)

For both sampling schemes, the exact time of sample collection will be recorded in the eCRF. The exact time of dosing on the day of the visit, 1 day prior to the visit and 2 days prior to the visit will be recorded in the eCRF by having the subject return a medication card on which the subject records this information.

Pharmacokinetic Samples Preparation and Transfer

Following collection, if the sample is not immediately centrifuged, it should be placed on crushed ice until centrifugation. Plasma will be separated by centrifugation (preferably with a refrigerated centrifuge at 4°C) at approximately 1500 g for 10 minutes, transferred to appropriately labelled polypropylene tubes and frozen at approximately -20°C or cooler. The processing of plasma samples should be completed within 30 minutes of collection. Labelling will include the study number (SB-480848/033), subject number, date, visit number and nominal sampling time. Samples will be stored at approximately -20°C or cooler until transported for analysis.

All plasma samples for assessment of darapladib PK will be transferred frozen on solid carbon dioxide to the central laboratory and subsequently to the Department of Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, King of Prussia, PA. Plasma samples will be assayed for darapladib using an approved method under the management of Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GlaxoSmithKline.

Pharmacodynamic Samples Preparation and Transfer

Following collection, if the sample is not immediately centrifuged, it should be placed on crushed ice until centrifugation. Plasma will be separated by centrifugation (preferably with a refrigerated centrifuge at 4°C) at approximately 1500 g for 10 minutes and transferred to appropriately labelled polypropylene tubes and frozen at approximately -20°C . The processing of plasma samples should be completed within 30 minutes of collection. Labelling will include the study number (SB-480848/033), subject number, date, visit number and nominal sampling time. Samples will be stored at approximately -20°C or cooler until transported for analysis.

All plasma samples for assessment of Lp-PLA₂ activity will be transferred frozen on solid carbon dioxide to the central laboratory. Plasma samples will be assayed for plasma Lp-PLA₂ activity using an approved method under the management of GlaxoSmithKline Pharmaceuticals.

Pharmacokinetic Analysis

Initially, a base population PK model (i.e., without inclusion of covariates) will be developed using data from the Phase III patients who contributed serial PK samples over a 24-hour period. The Phase III data may be combined with selected healthy volunteer data (e.g., studies using the same dose and administering the enteric coat, micronized free base tablet with food). Next, an exploratory analysis will be conducted on the

relationship between PK parameters from the base population PK model and various covariates. Significant covariate-parameter relationships will then be incorporated into the population PK model. An evaluation of the final population PK model will be performed. It is also planned to perform a non-compartmental analysis using the full concentration-time profiles collected from the Phase III patients. These results could be used to perform a posterior predictive check of the final population PK model.

Alternatively, in case a robust population PK model can not be developed, the non-compartmental analysis will provide AUC and Cmax data for darapladib in the target patient population which can be further explored for the influence of potential covariates. Data from the multiple-trough sampling design will be analyzed by mixed effects modeling.

PK data will be analyzed with the use of the nonlinear mixed effects modeling program (NONMEM). 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 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 interindividual 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.

Pharmacokinetic/Pharmacodynamic Analysis

The relationship between plasma concentrations of darapladib and plasma Lp-PLA₂ activity in humans has been explored using data obtained from previous studies. This concentration-effect relationship was best characterized by a sigmoidal inhibitory Emax model. This structural model was parameterized for IC50, darapladib plasma concentration causing 50% inhibition of plasma Lp-PLA₂ activity (ng/mL); E0, baseline plasma Lp-PLA₂ activity (nmol/min/mL); and γ , the Hill coefficient which describes the steepness of concentration-effect relationship. In the current study, a similar structural PK/PD model will be utilized to estimate parameters specific to the patient population of this study. Various statistical models will be examined to describe the variability of the data and parameterized as appropriate.

PK/PD data will be analyzed with the use of the nonlinear mixed effects modeling program (NONMEM). Model selection will be conducted using the same criteria as described above for the PK analyses. Covariates examined during the development of the population PK model will also be evaluated to assess their effects on darapladib PK/PD.

References

- Aarons, L., Population Pharmacokinetics: Theory and Practice. *Br J Clin Pharmacol* 1991; 32:669-70.

11.9. Appendix 9: Country Specific Requirements

Not applicable

11.10. Appendix 10 – Liver Safety Investigational Product Restart Guidelines

In Phase III-IV, investigational product (IP) restart may be considered for liver safety events with a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to a) within the normal range **OR** b) $\leq 1.5x$ baseline and ALT $<3xULN$.

Investigational Product (IP) Restart Guidelines

GSK Decision Process for IP Restart Approval or Disapproval (also see Figure 3)

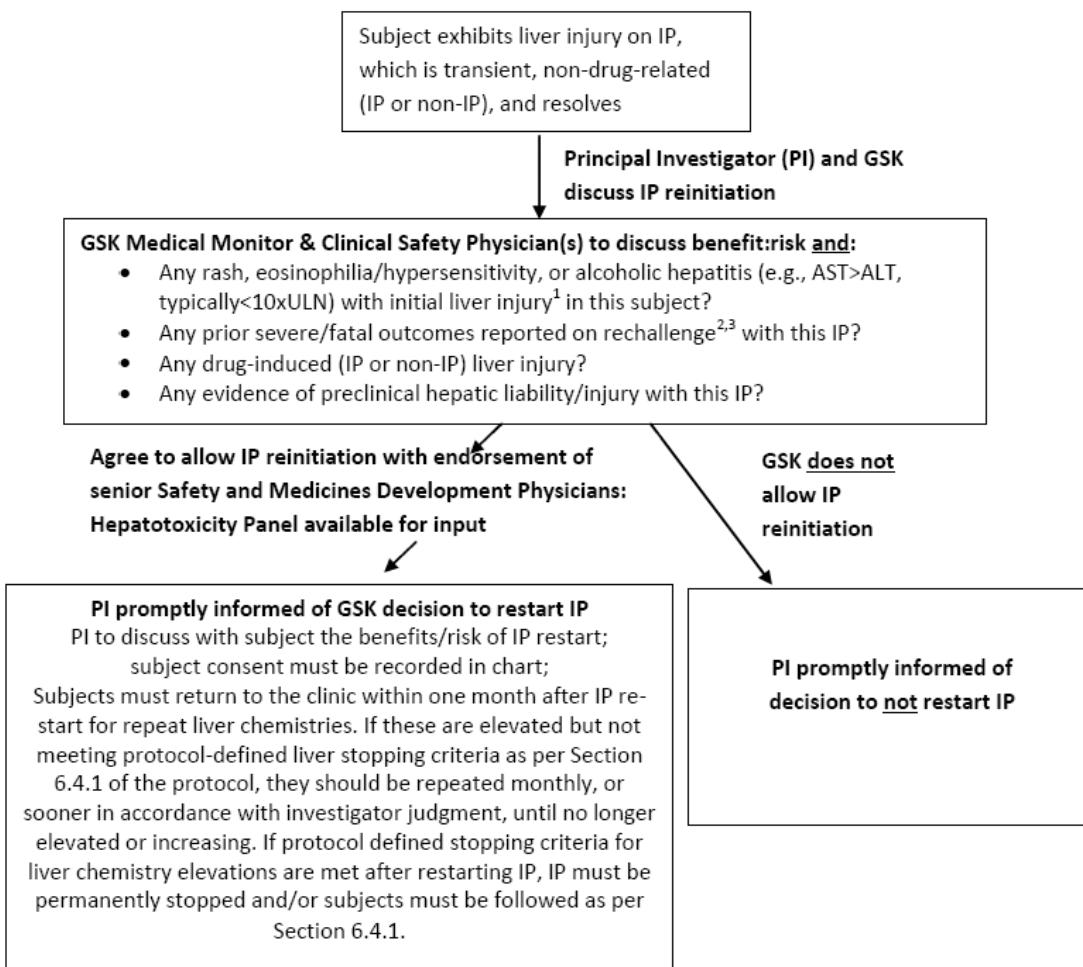
- Principal Investigator (PI) and GSK discuss IP re-initiation for a subject who exhibits liver chemistry elevation meeting IP stopping criteria, which is transient, non-drug-related (IP or non-IP), and resolves.
- GSK Medical Monitor & Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (See Table below).

Checklist for Phase III Investigational Product (IP) restart after well-explained liver injury (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), improving to liver chemistries a) within the normal range OR b) $\leq 1.5x$ baseline and ALT$<3xULN$.		
Do not restart if BOTH of the following questions are answered NO	Yes	No
Currently, are liver chemistries within the normal range?		
Currently, are liver chemistries $\leq 1.5x$ baseline <u>and</u> ALT$<3xULN$?		
Do not restart if any of the following questions are answered YES	Yes	No
Were any of the following risk factors present at initial liver injury?:		
• rash, eosinophilia, or hypersensitivity		
• drug-induced (IP or non-IP) liver injury		
• alcoholic hepatitis (e.g., AST>ALT, typically $<10xULN$)		

***Principal Investigator (PI) Actions**

- PI must discuss the benefits and risks of IP re-initiation with the subject.
- The subject must provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Subjects must return to the clinic within one month after IP re-start for repeat liver chemistries. If these are elevated but not meeting protocol-defined liver stopping criteria as per Section 6.4.1 of the protocol, they should be repeated monthly, or sooner in accordance with investigator judgment, until no longer elevated or increasing. If protocol defined stopping criteria for liver chemistry elevations are met after restarting IP, IP must be permanently stopped and/or subjects must be followed as per Section 6.4.1.
- The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.
- GSK to be notified of any adverse or serious adverse events, as per Section 6.4.2 and Section 6.4.3.

Figure 3 GSK Process for Investigational Product (IP) Restart Approvals



¹Andrade RJ. Expert Opin Drug Safe 2009;8:709-714 ²Papay JL. Regul Tox Pharm 2009;54:84-90 ³Hunt CM. Hepatol 2010;52:2116-2222

11.11. Appendix 11: Protocol Changes

Amendment 5 – Summary of Changes and Rationale

This is a global amendment and is applicable to all study sites.

The primary reason for this amendment is to change the primary efficacy endpoint from Major Adverse Cardiovascular Events (MACE: cardiovascular death, non-fatal MI, or non-fatal stroke) to the previous secondary endpoint of Major Coronary Events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia). Additional changes have been made to secondary and “other” endpoints to reflect the change to the primary endpoint

Rationale:

The Executive Steering Committee of the ongoing SOLID-TIMI-52 trial met to review data from the STABILITY (Study LPL100601) trial (similar design as Study SB-480848/033 except in a chronic CHD population) and made the recommendation to GSK that the primary endpoint of the SOLID-TIMI-52 trial (Study SB-480848/033) be revised to Major Coronary Events (CHD death, non-fatal myocardial infarction and urgent coronary revascularization for myocardial ischemia) from MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke). Specifically, this change would primarily remove both fatal and non-fatal stroke from the composite endpoint. In addition, emerging data from genetic studies and epidemiologic data show a lack of association between Lp-PLA₂ activity and risk of stroke. **The decision by GSK to follow the Executive Steering Committee's recommendation to amend the primary endpoint of the SOLID-TIMI 52 study was made prior to unblinding study data and without communication from the IDMC.**

CHANGES

PROTOCOL SUMMARY

Rationale

Summary

Original Text:

This Phase III outcomes study will compare the chronic effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care ≤ 30 days following presentation, on the incidence of major adverse cardiovascular events (MACE) in high risk patients following ACS.

Revised Text:

This Phase III outcome study was initially designed to compare the chronic effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care ≤ 30 days following presentation, on the incidence of major adverse cardiovascular events (MACE) in high risk patients following ACS. Prior to unblinding the study data, the primary endpoint of the study was amended and replaced with the

secondary endpoint of major coronary events (i.e., CHD death, non-fatal MI, urgent coronary revascularization for myocardial ischemia). Conduct of the study was based on the original primary endpoint of MACE.

Rationale for change to primary efficacy endpoint

The Executive Steering Committee of the ongoing SOLID-TIMI-52 trial met to review data from the STABILITY (Study LPL100601) trial (similar design as Study SB-480848/033 except in a chronic CHD population) and made the recommendation to GSK that the primary endpoint of the SOLID-TIMI-52 trial (Study SB-480848/033) be revised to Major Coronary Events (CHD death, non-fatal myocardial infarction and urgent coronary revascularization for myocardial ischemia) from MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke). Specifically, this change would primarily remove both fatal and non-fatal stroke from the composite endpoint. In addition, emerging data from genetic studies and epidemiologic data show a lack of association between Lp-PLA₂ activity and risk of stroke. **The decision by GSK to follow the Executive Steering Committee's recommendation to amend the primary endpoint of the SOLID-TIMI 52 study was made prior to unblinding study data and without communication from the IDMC.**

PROTOCOL SUMMARY

Objective(s)

Primary objective

Original Text:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of MACE (i.e., CV death, non-fatal MI, non-fatal stroke).

Revised Text:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia).

PROTOCOL SUMMARY

Objective(s)

Secondary objectives

Original Text:

The secondary objectives are to evaluate the efficacy of darapladib on major and total coronary events (including CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina), individual components of MACE and all-cause mortality. Additional safety and efficacy parameters, including relations to and changes of biomarkers of CV risk, genetics, health economic outcomes,

and adverse events (AEs), will also be evaluated.

Revised Text:

The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters, including relations to and changes of biomarkers of CV risk, genetics, health economic outcomes, and adverse events (AEs), will also be evaluated.

PROTOCOL SUMMARY

Study Design

Original Text:

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event-driven trial. Subjects with ACS and receiving standard of care will be randomized 1:1 to once daily doses of Darapladib Enteric Coated Tablets, 160 mg or placebo. The duration of the study will be determined by the rate of first occurrence of events that comprise the primary MACE composite. The study will be terminated when approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred.

Revised Text:

The primary endpoint of the study was amended prior to unblinding the study data. Conduct of the study was based on the original primary endpoint of MACE. Data collection in the study was not affected by this change since the new primary endpoint was previously a secondary endpoint.

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event-driven trial. Subjects with ACS and receiving standard of care will be randomized 1:1 to once daily doses of Darapladib Enteric Coated Tablets, 160 mg or placebo. The duration of the study will be determined by the rate of first occurrence of events that comprise the MACE composite. The study will be terminated when approximately 1500 reports of first occurrence of MACE have occurred.

PROTOCOL SUMMARY

Study Endpoints/Assessments

Original Text:

The primary endpoint is the time to the first occurrence of any component of the composite of MACE (i.e., CV death, non-fatal MI, non-fatal stroke) in an ACS patient population.

Secondary endpoints include:

- The composite measure of **major coronary events** that include CHD death, non-fatal MI or urgent coronary revascularization for myocardial ischemia.
- The composite measure of **total coronary events** that include CHD death, non-fatal MI, hospitalization for UA, or any coronary revascularization procedure (excluding percutaneous coronary intervention [PCI] planned prior to randomization but performed after randomization).
- **Individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]).
- Any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- All cause mortality.

Revised Text:

The primary endpoint is the time to the first occurrence of any component of the composite of **major coronary events** that include CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia in an ACS patient population.

Secondary endpoints include:

- The composite measure of **MACE** that includes CV death, non-fatal MI, or non-fatal stroke.
- **Individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]).
- **Individual components of major coronary events** (CHD death, MI [fatal and non-fatal], urgent coronary revascularization for myocardial ischemia).
- The composite measure of **total coronary events** that include CHD death, non-fatal MI, hospitalization for UA, or any coronary revascularization procedure (excluding percutaneous coronary intervention [PCI] planned prior to randomization but performed after randomization).
- Any coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).
- Any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- The composite of CHD death and non-fatal MI
- All cause mortality.

Section 1.2 – Rationale

Original Text:

This Phase III outcomes study will compare the effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care, on the incidence of major adverse cardiovascular events (MACE) in patients with ACS.

Revised Text:

This Phase III outcome study was initially designed to compare the chronic effects of Darapladib Enteric Coated Tablets, 160 mg versus placebo, when added to the standard of care ≤ 30 days following presentation, on the incidence of major adverse cardiovascular events (MACE) in high risk patients following ACS. Prior to unblinding the study data, the primary endpoint of the study was amended and replaced with the secondary endpoint of major coronary events (i.e., CHD death, non-fatal MI, urgent coronary revascularization for myocardial ischemia). Conduct of the study was based on the original primary endpoint of MACE.

Rationale for change to primary efficacy endpoint

The Executive Steering Committee of the ongoing SOLID-TIMI-52 trial met to review data from the STABILITY (Study LPL100601) trial (similar design as Study SB-480848/033 except in a chronic CHD population) and made the recommendation to GSK that the primary endpoint of the SOLID-TIMI-52 trial (Study SB-480848/033) be revised to Major Coronary Events (CHD death, non-fatal myocardial infarction and urgent coronary revascularization for myocardial ischemia) from MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke). Specifically, this change would primarily remove both fatal and non-fatal stroke from the composite endpoint. In addition, emerging data from genetic studies and epidemiologic data show a lack of association between Lp-PLA₂ activity and risk of stroke. **The decision by GSK to follow the Executive Steering Committee's recommendation to amend the primary endpoint of the SOLID-TIMI 52 study was made prior to unblinding study data and without communication from the IDMC.**

Section 2 – OBJECTIVE(S)

Original Text:

Primary objective:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of MACE (i.e., CV death, non-fatal MI, non-fatal stroke).

Secondary objectives:

The secondary objectives are to evaluate the efficacy of darapladib on major and total coronary events (including CHD death, non-fatal MI, urgent and non-urgent coronary

revascularization, or hospitalization for UA), individual components of MACE and all-cause mortality. Additional safety and efficacy parameters including relations to and changes of biomarkers of CV risk, health economic outcomes, and adverse events (AEs) will also be evaluated.

Revised Text:

Primary objective:

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared with placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia).

Secondary objectives:

The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters, including relations to and changes of biomarkers of CV risk, health economic outcomes, and adverse events (AEs), will also be evaluated.

Section 3.1 – Study Design

Original Text:

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event driven trial (See Figure 2). The duration of the study will be determined by the rate of first occurrence of clinical events that comprise the primary endpoint (the composite of MACE). The study will be terminated when it is projected that approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred. Based on current assumptions, the median treatment duration is anticipated to be approximately 3 years.

All subjects are to be followed until the termination of the study, regardless of whether they permanently discontinue treatment with investigational product (IP) or experience a non-fatal MACE. Ideally, subjects will continue treatment with IP after experiencing a MACE.

Revised Text:

The primary endpoint of the study was amended prior to unblinding the study data. Conduct of the study was based on the original primary endpoint of MACE. Data collection in the study was not affected by this change since the new primary endpoint was previously a secondary endpoint.

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event driven trial (See Figure 2). The duration of the study will be determined by the rate of first occurrence of clinical events that comprise the composite of MACE. The study will be terminated when it is projected that approximately 1500 reports of first occurrence of MACE have occurred. Based on current assumptions, the median treatment duration is anticipated to be approximately 3 years.

All subjects are to be followed until the termination of the study, regardless of whether they permanently discontinue treatment with investigational product (IP) or experience a non-fatal MACE. Ideally, subjects will continue treatment with IP after experiencing a MACE.

Section 3.1 – Study Design

End of Study (EOS)

When it is projected that approximately 1500 reports of first occurrence of MACE (~~primary endpoint~~) have occurred, the sponsor will notify investigators to begin scheduling end of study contacts for all their study subjects within a defined EOS period.

Section 3.2 – Discussion of Design

Study Design

Original Text:

This study is a clinical outcomes study. The primary clinical endpoint, MACE (defined as composite of CV death, non-fatal MI and non-fatal stroke), is a well-established endpoint for CV trials. An external Independent Data Monitoring Committee (IDMC) will monitor safety in the study and an independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina, and heart failure requiring hospitalization).

Revised Text:

This study is a clinical outcomes study. The original primary clinical endpoint, MACE (defined as composite of CV death, non-fatal MI and non-fatal stroke), is a well-established endpoint for CV trials. The primary endpoint of the study was amended to major coronary events, defined as the composite of CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia, prior to unblinding the study data.

An external Independent Data Monitoring Committee (IDMC) will monitor safety in the study and an independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina and heart failure requiring hospitalization).²⁸ Therefore all components of major coronary events were also adjudicated by the CEC.

²⁸ **NOTE:** Details of the scope and criteria for clinical adjudication by the CEC are delineated in the separate charter of the CEC.

Section 3.2 – Discussion of Design**Dose Rationale**

Original Text:

The goal of treatment with darapladib is to achieve near maximal inhibition of Lp-PLA₂ in the plaque with a resultant reduction in the risk of MACE, while maintaining an acceptable safety and tolerability profile.

Revised Text:

The goal of treatment with darapladib is to achieve near maximal inhibition of Lp-PLA₂ in the plaque with a resultant reduction in the risk of major coronary events, while maintaining an acceptable safety and tolerability profile

Section 4.4 - Stopping IP Early or Withdrawal from the Study**Data Collection Following Withdrawal of Consent for Further Participation in the Study**

The checklist needs to be completed for all randomized subjects who have withdrawn consent, even for those who withdrew prior to ~~this amendment~~ (Amendment 3)

Section 5.1 - Investigational Product and Reference Therapy

Treatment will continue until it is projected that approximately 1500 reports of first occurrence of MACE (~~primary endpoint~~) have occurred.

Section 6.3 – Efficacy

Original Text:

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina and heart failure requiring hospitalization).

Revised Text:

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina and heart failure requiring hospitalization).²⁹ Therefore all components of major coronary events were also adjudicated by the CEC.

Section 6.3.1 - Primary Efficacy Endpoint

Original Text:

The primary efficacy endpoint is the time to the first occurrence of any component of **the composite of major adverse cardiovascular events (MACE: CV death, non-fatal MI,**

²⁹ **NOTE:** Details of the scope and criteria for clinical adjudication by CEC are delineated in the separate charter of CEC.

or non-fatal stroke) in an ACS population treated with Darapladib Enteric Coated Tablets, 160 mg compared with placebo.

Revised Text:

The primary efficacy endpoint is the time to the first occurrence of any component of **the composite of major coronary events that includes CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia** in an ACS population treated with Darapladib Enteric Coated Tablets, 160 mg compared with placebo.

Section 6.3.1.1

Original Text:

6.3.1.1 Cardiovascular Death

CV death is defined as death due to documented CV cause. Causes of CV deaths include but are not limited to deaths resulting from stroke, arrhythmia, sudden death (witnessed or unwitnessed), MI, heart failure, pulmonary embolism, PAD or complications of a CV procedure. Additionally, deaths not clearly attributable to non-CV causes will be considered CV deaths.

Revised Text:

6.3.1.1 Coronary Heart Disease Death

CHD death is defined as the occurrence of a fatal MI, death caused by documented cardiac arrest (e.g., ventricular fibrillation or other lethal arrhythmia without known secondary causes), death resulting from heart failure in a patient with known CHD, death from other forms of acute or chronic CHD, unwitnessed death of unknown origin or sudden death.

Section 6.3.1.3

Original Text:

6.3.1.3 Stroke

Stroke is defined as the presence of **a new focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting >24 hours, or results in death (in <24 hours)**. It is strongly recommended that neuroimaging, such as computed tomography (CT) scan or magnetic resonance imaging (MRI), be performed to confirm diagnosis. In the absence of neuroimaging, additional functional deficit must be documented by a change in the modified Rankin Score [Banks, 2007].

If neurologic symptoms last <24 hours, new brain infarction has to be confirmed by diffusion-weighted MRI showing the presence of a new brain infarct. Alternate forms of neuroimaging will be accepted only if it can be demonstrated that a defect is new. In addition, location of a defect must be consistent with the observed neurological symptoms. Confirmed retinal arterial ischemic event (embolism, infarction) will be considered a stroke. Stroke will be further classified as ischemic, hemorrhagic, ischemic with hemorrhagic conversion, or type uncertain.

Revised Text:

6.3.1.3 Urgent Coronary Revascularization for Myocardial Ischemia

Urgent coronary revascularization for myocardial ischemia is defined as ischemic discomfort at rest that prompts coronary revascularization (PCI or CABG) during the same hospitalization or resulting in hospital transfer for the purpose of coronary revascularization. PCI is defined as any attempt at revascularization even if not successful (e.g., angioplasty, atherectomy or stenting).

Section 6.3.2 - Secondary Efficacy Endpoints

Original Text:

- The composite measure of **major coronary events** that include the first occurrence of CHD death,³⁰ non-fatal MI³¹ or urgent coronary revascularization for myocardial ischemia³² in darapladib-treated subjects compared with placebo
- The composite measure of **total coronary events** that include the first occurrence of CHD death, non-fatal MI, hospitalization for unstable angina,³³ or any coronary revascularization procedure (excluding PCI planned prior to randomization but performed after randomization) in darapladib-treated subjects as compared with placebo.
- The **individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]) in darapladib-treated subjects as compared with placebo.^{34,35}

³⁰ **Note:** CHD death is defined as the occurrence of a fatal MI, death caused by documented cardiac arrest (e.g., ventricular fibrillation or other lethal arrhythmia without known secondary causes), death resulting from heart failure in a patient with known CHD, death from other forms of acute or chronic CHD, unwitnessed death of unknown origin or sudden death.

³¹ **Note:** See definition of MI in Section 6.3.1.2.

³² **Note:** Urgent coronary revascularization for myocardial ischemia is defined as ischemic discomfort at rest that prompts coronary revascularization (PCI or CABG) during the same hospitalization or resulting in hospital transfer for the purpose of coronary revascularization. PCI is defined as any attempt at revascularization even if not successful (e.g., angioplasty, atherectomy or stenting).

³³ **Note:** Hospitalization for unstable angina is defined as one of the following but not fulfilling the criteria for MI: (a) ischemic discomfort at rest associated with ECG changes leading to hospitalization OR (b) ischemic discomfort at rest regardless of ECG changes leading to hospitalization AND revascularization during the same admission OR (c) ischemic discomfort at rest in hospital associated with ECG changes OR (d) ischemic discomfort at rest in hospital without ECG changes resulting in revascularization during the same admission. The event will not be considered unstable angina if, after invasive/non-invasive testing or other diagnostic testing, the discomfort is found not to be caused by myocardial ischemia. Details of ECG changes indicative of ischemia are described in the CEC charter and in the eCRF.

³⁴ **Note:** See definition of MI in Section 6.3.1.2. In addition, different types of MI as described in the Universal Definition of MI [Thygesen, 2007] will be ascertained. Detailed definition and clinical criteria are provided in the CEC charter.

³⁵ **Note:** See definition of stroke in Section 6.3.1.3.

- The first occurrence of any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- All cause mortality.

Revised Text:

- The composite measure of **MACE** that includes the first occurrence of CV death,³⁶ non-fatal MI³⁷ or non-fatal stroke³⁸ in darapladib-treated subjects compared with placebo
- The **individual components of MACE** (CV death, MI [fatal and non-fatal], stroke [fatal and non-fatal]) in darapladib-treated subjects as compared with placebo.
- **Individual components of major coronary events** (CHD death³⁹, MI [fatal and non-fatal], urgent coronary revascularization for myocardial ischemia⁴⁰)
- The composite measure of **total coronary events** that include the first occurrence of CHD death, non-fatal MI, hospitalization for unstable angina,⁴¹ or any coronary revascularization procedure (excluding PCI planned prior to randomization but performed after randomization) in darapladib-treated subjects as compared with placebo.

³⁶ **Note:** CV death is defined as death due to documented CV cause. Causes of CV deaths include but are not limited to deaths resulting from stroke, arrhythmia, sudden death (witnessed or unwitnessed), MI, heart failure, pulmonary embolism, PAD or complications of a CV procedure. Additionally, deaths not clearly attributable to non-CV causes will be considered CV deaths.

³⁷ **Note:** See definition of MI in Section 6.3.1.2.

³⁸ **Note:** Stroke is defined as the presence of a new focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting >24 hours, or results in death (in <24 hours). It is strongly recommended that neuroimaging, such as computed tomography (CT) scan or magnetic resonance imaging (MRI), be performed to confirm diagnosis. In the absence of neuroimaging, additional functional deficit must be documented by a change in the modified Rankin Score [Banks, 2007]. If neurologic symptoms last <24 hours, new brain infarction has to be confirmed by diffusion-weighted MRI showing the presence of a new brain infarct. Alternate forms of neuroimaging will be accepted only if it can be demonstrated that a defect is new. In addition, location of a defect must be consistent with the observed neurological symptoms. Confirmed retinal arterial ischemic event (embolism, infarction) will be considered a stroke. Stroke will be further classified as ischemic, hemorrhagic, ischemic with hemorrhagic conversion, or type uncertain.

³⁹ Note: See definition of CHD Death in Section 6.3.1.1

⁴⁰ Note: See definition of urgent coronary revascularization for myocardial ischemia in Section 6.3.1.3

⁴¹ **Note:** Hospitalization for unstable angina is defined as one of the following but not fulfilling the criteria for MI: (a) ischemic discomfort at rest associated with ECG changes leading to hospitalization OR (b) ischemic discomfort at rest regardless of ECG changes leading to hospitalization AND revascularization during the same admission OR (c) ischemic discomfort at rest in hospital associated with ECG changes OR (d) ischemic discomfort at rest in hospital without ECG changes resulting in revascularization during the same admission. The event will not be considered unstable angina if, after invasive/non-invasive testing or other diagnostic testing, the discomfort is found not to be caused by myocardial ischemia. Details of ECG changes indicative of ischemia are described in the CEC charter and in the eCRF.

- Any coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).
- The first occurrence of any component of the composite of all-cause mortality, non-fatal MI, or non-fatal stroke.
- The composite of CHD death and non-fatal MI
- All cause mortality.

Section 6.3.3 – Others

Original Text:

- Total incidence of first and subsequent CV events comprising MACE.
- Urgent coronary revascularization for myocardial ischemia.⁴²
- All coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).
- Heart failure requiring hospitalization.⁴³
- **Total vascular events** that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary [excluding PCI planned prior to randomization but performed after randomization]), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo. NOTE: Unplanned hospitalization for a new peripheral arterial ischemic event should be reported as the endpoint “Hospitalization for a non-coronary ischemic event”. This includes patients with acute limb or visceral ischemia, including acute ischemia caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure.
- **The composite of total coronary events** (CHD death, non-fatal MI, hospitalization for unstable angina, or any coronary revascularization procedure [excluding PCI planned prior to randomization but performed after randomization]) in darapladib-treated subjects compared with placebo, **excluding target lesion revascularization** (i.e., restenosis) in subjects treated with PCI prior to randomization.
- New onset diabetes mellitus (post-randomization diagnosis is based on investigator judgment).
- Chronic inhibition of plasma Lp-PLA₂ activity (see Table 1, Table 2, and Table 3 for more information).

⁴² **Note:** See definition of urgent coronary revascularization for myocardial ischemia in Section 6.3.2.

⁴³ **Note:** Heart failure requiring hospitalization is defined as admission to hospital or attendance at an acute healthcare facility for administration of intravenous diuretic treatment, escalation of diuretic doses, and/or inotropes. Confirmation of heart failure diagnosis is required by chest imaging demonstrating pulmonary congestion or edema [Held, 2007] OR, in patients *without* available chest imaging, at least one of the following: pulmonary edema (i.e. rales >1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure >18 mm Hg, or BNP >500 pg/ml (or NT-terminal prohormone BNP >2500 pg/ml) [Maisel, 2001].

- Health care resources utilization (i.e. hospitalization and major procedures). See Section 6.5 for more information.

Revised Text:

- Total incidence of first and subsequent coronary events comprising major coronary events.
- Total incidence of first and subsequent CV events comprising MACE.
- Heart failure requiring hospitalization.⁴⁴
- **Total vascular events** that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary [excluding PCI planned prior to randomization but performed after randomization]), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo. NOTE: Unplanned hospitalization for a new peripheral arterial ischemic event should be reported as the endpoint “Hospitalization for a non-coronary ischemic event”. This includes patients with acute limb or visceral ischemia, including acute ischemia caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure.
- **The composite of total coronary events** (CHD death, non-fatal MI, hospitalization for unstable angina, or any coronary revascularization procedure [excluding PCI planned prior to randomization but performed after randomization]) in darapladib-treated subjects compared with placebo, **excluding target lesion revascularization** (i.e., restenosis) in subjects treated with PCI prior to randomization.
- New onset diabetes mellitus (post-randomization diagnosis is based on investigator judgment).
- Chronic inhibition of plasma Lp-PLA₂ activity (see Table 1, Table 2, and Table 3 for more information).
- Health care resources utilization (i.e. hospitalization and major procedures). See Section 6.5 for more information.

Section 6.4.9 - Events of Cancer and GI Polyps/Neoplasms

Data collected

Original Text:

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will

⁴⁴ Note: Heart failure requiring hospitalization is defined as admission to hospital or attendance at an acute healthcare facility for administration of intravenous diuretic treatment, escalation of diuretic doses, and/or inotropes. Confirmation of heart failure diagnosis is required by chest imaging demonstrating pulmonary congestion or edema [Held, 2007] OR, in patients *without* available chest imaging, at least one of the following: pulmonary edema (i.e. rales >1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure >18 mm Hg, or BNP >500 pg/ml (or NT-terminal prohormone BNP >2500 pg/ml) [Maisel, 2001].

be recorded from randomization to the end of the study.

Revised Text:

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will be recorded from randomization to the end of the study. NOTE: As per a country-specific amendment in France, subjects in France who are diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis) must immediately discontinue IP. In the event that a subject permanently discontinues IP, every effort should be made by the investigator to follow the subject to assess study endpoints including MACE (See Section 4.4. "Stopping IP Early or Withdrawal from the Study").

Section 8.1 – Hypotheses

The primary analysis will test the following hypotheses:

- Null hypothesis: Hazard ratio for MACE major coronary events for darapladib relative to placebo is equal to one. This is equivalent to a reduction in risk equal to zero.
- Alternative hypothesis: Hazard ratio for MACE major coronary events for darapladib relative to placebo is not equal to one (i.e., two-sided test). This is equivalent to a reduction in risk not equal to zero.

Section 8.2.1 – Sample Size Assumptions

Original Text:

This event driven study is designed to have 90% power to detect a 15.5% reduction in risk of primary efficacy MACE event (hazard ratio=0.845) for subjects treated with darapladib compared to placebo on top of a background of standard care. Assuming a placebo event rate of approximately 7.5% for the first year and 3.5% per year thereafter, with an overall type I error rate (alpha level) of 5%, a total of 1500 primary efficacy events are required to achieve approximately 90% power. Components of the primary composite endpoint are expected to make up approximately 20% events from CV death, 60% events from non-fatal MI, and 20% events from non-fatal stroke. All subjects will be followed until the required total number of events occurs.

Revised Text:

This event driven study is designed to have 90% power to detect a 15.5% reduction in risk of MACE event (hazard ratio=0.845) for subjects treated with darapladib compared to placebo on top of a background of standard care. Assuming a placebo event rate of approximately 7.5% for the first year and 3.5% per year thereafter, with an overall type I error rate (alpha level) of 5%, a total of 1500 MACE are required to achieve approximately 90% power. Components of MACE are expected to make up approximately 20% events from CV death, 60% events from non-fatal MI, and 20% events from non-fatal stroke. All subjects will be followed until the required total number of events occurs. **NOTE: Because the primary endpoint was changed after**

the required number of MACE events was achieved, sample size calculations were not changed to reflect the new primary endpoint of major coronary events.

Section 8.3.1 - Analysis Populations

The primary population for analysis of ~~MACE~~ major coronary events and secondary time-to-event outcomes will be the Intent-to-Treat (ITT) Population, consisting of all randomized subjects.

Section 8.3.2.1 - Primary Comparisons of Interest

The primary comparison of interest is the comparison of hazard rates of ~~MACE~~ major coronary events for darapladib vs. placebo (i.e. the Hazard Ratio).

Section 8.3.2.2 - Sensitivity Analyses

Further sensitivity analyses of the primary efficacy endpoint will also be performed to assess the robustness of the primary results.

- An analysis of only on-treatment ~~MACE~~ major coronary events will be performed in the ITT population.

Section 8.3.4.1 - Efficacy Analyses

Original Text:

The primary efficacy outcome is MACE. Secondary outcomes include components of MACE (i.e., CV death, stroke, MI), all cause mortality, major coronary events, total coronary events and the composite of all mortality, MI or stroke.

Revised Text:

The primary efficacy outcome is major coronary events (i.e., CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia). Secondary outcomes include major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, or non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality.

Section 8.3.4.3 - Data Derivations

Derived and Transformed Data

For time to event endpoints (e.g., ~~MACE~~ major coronary events), an event time (days) will be derived as the date the event occurred minus the date of randomization + 1 day.

Section 9.4 - Study and Site Closure

When it is projected that approximately 1500 reports of first occurrence of MACE (~~primary endpoint~~) have occurred, the investigators will be notified to contact all subjects to schedule an End-of-Treatment visit to take place as soon as possible.

Section 9.8 - Clinical Endpoint Committee

Original Text:

An independent CEC will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for UA, and heart failure requiring hospitalization).

Revised Text:

An independent CEC will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for UA, and heart failure requiring hospitalization). Therefore all components of major coronary events were also adjudicated by the CEC.

Section 11.9 - Appendix 9: Country Specific Requirements

Original Text:

No country-specific requirements exist.

Revised Text:

Not applicable

Amendment 4 – Summary of Changes and Rationale

This **Country-Specific amendment** applies to all study sites participating in Study SB-480848/033 **in France**. Participating study sites in countries outside of France are not affected by this amendment.

The ANSM (French regulatory authority) requires that subjects in France currently enrolled in the Phase III trials with darapladib immediately discontinue investigational product (IP) if they are diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis).

CHANGE:**Section 6.4.9 - Events of Cancer and GI Polyps/Neoplasms****Data Collected (paragraph 2)**Original Text:

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will be recorded from randomization to the end of the study.

Revised Text:

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will be recorded from randomization to the end of the study. **NOTE: In France, subjects diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis) must immediately discontinue IP. In the event that a subject permanently discontinues IP, every effort should be made by the investigator to follow the subject to assess study endpoints including MACE (See Section 4.4. “Stopping IP Early or Withdrawal from the Study”).**

Amendment 3 – Summary of Changes and Rationale

This is a global amendment and is applicable to all study sites.

The primary intent is to allow increased collection of data on new cancer, recurrence of cancer, or progression of cancer; and adjudication of all GI neoplasms (malignant and benign), and all GI polyps (malignant, benign, and non-neoplastic).

Additional changes are summarized below.

- **Add PRIMARY CONTACTS FOR EXTERNAL COMMITTEES WITH OVERSIGHT OR ADMINISTRATIVE RESPONSIBILITIES.**
This information was inadvertently omitted from the previous protocol amendment (Amendment #2).
- Request a final clinic visit for subjects who permanently discontinued IP prior to the end of the study.
- Correct text to be consistent regarding use of telephone and clinic visits to follow subjects who permanently discontinue IP prior to the end of the study.
- Clarify data collection for subjects who have discontinued IP and are in post-IP follow-up.
- Allow a subject who met liver chemistry stopping criteria to restart IP if liver chemistries have improved to within the normal range, even if >1.5 x Baseline.
- Clarify completion of Follow-up checklist for subjects who withdrew consent for participation in the study.

List of Protocol Changes with Rationale for Each

1. **Allow increased collection of data on new cancer, recurrence of cancer, or progression of cancer; and adjudication of all GI neoplasms (malignant and benign), and all GI polyps (malignant, benign, and non-neoplastic).**

Rationale:

Darapladib was given by oral gavage to male and female rodents starting from before sexual maturation and continuing every day throughout their lifetime for up to 2 years. Data from these studies recently became available. Overall, the data suggest drug-related increases in the incidence of adenomas and/or adenocarcinomas of the jejunum in male mice and male rats given higher doses of darapladib. Further details regarding these data can be found in Section 2.1 of the 31/July/2012 *Supplement 02 to Darapladib Investigator Brochure Version 8*.

The Independent Data Monitoring Committee for this study and the second Phase III study (Study LPL100601) has reviewed these data and re-reviewed the safety data, including reports of tumors in study subjects. Following this review, the IDMC recommended that the trials continue without any changes.

This change will allow a more thorough review of neoplasms reported in this study.

Add GI – Gastrointestinal to LIST OF ABBREVIATIONS**Section 3.1 (Study Design/Follow-up Phase)****Original Text:**

At the end of the study, a Follow-up Visit will be scheduled to occur 35 ± 7 days after the final dose of IP. If all AEs and serious adverse events (SAEs) have resolved at the time of the Follow-up Visit, no further AE data will be collected. In general, unless the investigator and sponsor discuss an alternative, ongoing AE and SAE data will be collected up to 35 days after the last dose of IP or until the Follow-up Visit, whichever is longer, after which no further data will be collected. Before scheduling any additional clinic visits after the Follow-up Visit, the investigator should first discuss the situation with the sponsor.

Revised Text:

At the end of the study, a Follow-up Visit will be scheduled to occur 35 ± 7 days after the final dose of IP. If all AEs and serious adverse events (SAEs) have resolved at the time of the Follow-up Visit, no further AE data (except for those events described in Section 6.4.6 and Section 6.4.9) will be collected. In general, unless the investigator and sponsor discuss an alternative, ongoing AE and SAE data will be collected up to 35 days after the last dose of IP or until the Follow-up Visit, whichever is longer, after which no further data (except for those events described in Section 6.4.6 and Section 6.4.9) will be collected. Before scheduling any additional clinic visits after the Follow-up Visit, the investigator should first discuss the situation with the sponsor.

Section 4.4**Original Text:**

Subjects have the right to stop taking IP before the end of the study or withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject may also be asked to stop IP at the investigator's discretion. **In the event that a subject permanently discontinues IP before the end of the study, the investigator should continue to follow the subject by telephone or in clinic to assess study endpoints including MACE (see Section 6.3). In addition investigator should continue to report SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (see Section 6.4.6).**

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (See Section 6.4.6). NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of the study.

Revised Text:

Subjects have the right to stop taking IP before the end of the study or withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject may also be asked to stop IP at the investigator's discretion. **In the event that a subject permanently discontinues IP before the end of the study, the investigator should continue to follow the subject by telephone or in clinic to assess study endpoints including MACE (see Section 6.3). In addition investigator should continue to report SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (see Section 6.4.6). Events of cancer and gastrointestinal (GI) polyps/neoplasms should be reported until the end of the study (as described in Section 6.4.9).**

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication (See Section 6.4.6) as well as AEs/SAEs of cancer and GI polyps/neoplasms (See Section 6.4.9) should also be reported. **NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of the study.**

Table 2

Add row to Table 2 for "Events of cancer and GI polyps/neoplasms" with footnote #11 "See Section 6.4.9 for details regarding events of cancer and GI polyps/neoplasms"

Add the following at the end of Section 6.4.6 (Time Period and Frequency of Detecting AEs and SAEs):**Collection of Events of Cancer and GI Polyps/Neoplasms**

Events of cancer and GI polyps/neoplasms will be reported as AEs or SAEs according to the cancer reporting period described in Section 6.4.9.

Add Section 6.4.9 – Events of Cancer and GI Polyps/Neoplasms**Timing of Collection for Events of cancer and GI polyps/neoplasms**

Collection of events of cancer and GI polyps/neoplasms will be extended to include the period off IP for subjects who have permanently discontinued IP. These events will be recorded from randomization until the end of the study.

Data Collected

Reports of new cancer, recurrence of cancer, or progression of cancer will be recorded in all randomized subjects. Progression will be defined as spread to local lymph nodes or contiguous organs, as well as metastases. Benign GI polyps and all other benign GI neoplasms will also be recorded.

GI medical history including specific risk factors for intestinal cancers will be recorded in all randomized subjects. All upper and lower GI endoscopies and GI capsule studies will be recorded from randomization to the end of the study.

For “events of cancer and GI polyps/neoplasms” recorded prior to institution of Amendment #3, study sites should provide the same requested information as for new cancers, neoplasms or polyps.

Adjudication of GI events

All GI neoplasms (malignant and benign) and all GI polyps (malignant, benign, and non-neoplastic) will undergo adjudication. GI is defined as the entire tract from the esophagus to rectum as well as the liver, biliary system/gall bladder and pancreas. The neoplasms include primary GI neoplasms and neoplasms metastatic to the GI system. Anal cancers will also undergo CEC adjudication to ensure misclassification has not occurred.

Section 9.8

Original Text:

An independent CEC will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for UA, and heart failure requiring hospitalization). Procedures for adjudicating events are described in the CEC charter, which is available upon request.

Revised Text:

An independent CEC will review and adjudicate all clinical events that constitute MACE (i.e., CV death, non-fatal MI, non-fatal stroke), and other selected key endpoints (e.g., CHD death, urgent coronary revascularization for myocardial ischemia, hospitalization for UA, and heart failure requiring hospitalization). The CEC will also adjudicate all reported cases of polyps or neoplasms that involve the GI tract (entire tract from the esophagus to rectum as well as the liver, biliary system/gall bladder and pancreas) as described in Section 6.4.9. In addition, anal cancers will undergo CEC adjudication to ensure misclassification has not occurred. Procedures for adjudicating events are described in the CEC charter, which is available upon request.

1. Add PRIMARY CONTACTS FOR EXTERNAL COMMITTEES WITH OVERSIGHT OR ADMINISTRATIVE RESPONSIBILITIES.

Rationale:

This information was inadvertently omitted from the previous protocol amendment (Amendment #2).

Text added after SPONSOR INFORMATION PAGE:

**PRIMARY CONTACTS FOR EXTERNAL COMMITTEES WITH
OVERSIGHT OR ADMINISTRATIVE RESPONSIBILITIES FOR
STUDY SB-480848/033**

Steering Committee Chair

Eugene Braunwald, MD, MACC
TIMI Study Group
350 Longwood Ave
1st Floor
Boston MA 02115

Clinical Endpoint Committee Chair

Stephen Wiviott, MD
TIMI Study Group
350 Longwood Ave
1st Floor
Boston MA 02115

Independent Data Monitoring Committee Chair

Rory Collins, MB, BS
Clinical Trial Service Unit
Richard Doll Building
Old Road Campus
Roosevelt Drive
Oxford OX3 7LF
United Kingdom.

2. Request a final clinic visit for subjects who permanently discontinued IP prior to the end of the study.

Rationale:

This visit allows a final clinic visit to assess efficacy and safety before the subject completes the study.

Add EOS – End of Study to LIST OF ABBREVIATIONS

Section 3.1 (Study Design/End-of-Treatment)

Original Text:

End of Treatment (EOT)

When it is projected that approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred, the sponsor will notify investigators to begin scheduling end of study contacts (i.e., EOT visits for subjects who have not

discontinued IP, final telephone calls for subjects in phone or third party Follow-up, and survival status searches for subjects who have withdrawn from the study or are lost to Follow-up) for all their study subjects in accordance with a pre-defined study close-out period. Subjects will be instructed to continue taking IP as usual until the day before this visit occurs. Subjects will return all remaining IP at this visit.

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed in clinic at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance).

Revised Text:**End of Treatment (EOT)**

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed in clinic at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance).

End of Study (EOS)

When it is projected that approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred, the sponsor will notify investigators to begin scheduling end of study contacts for all their study subjects within a defined EOS period.

The EOS contact should be scheduled within the protocol-defined visit intervals (e.g., ± 20 days from the scheduled clinic visit) based on the original visit schedule, with the additional requirement that the visit/contact occurs within the pre-defined EOS period for all subjects. In addition, survival status searches for subjects who are lost to follow-up or who withdrew consent for further participation in the study should be conducted during the EOS period where possible.

Every effort should be made to conduct the EOS contact in the clinic (i.e., face to face) during the EOS period for all subjects who are either on treatment, in post-IP phone/clinic follow-up, or in third party follow-up. Procedures for the EOS contact will be performed accordingly based upon whether the visit represents an EOT, Follow-up, or other visit as previously defined in the protocol (see Table 2 and Table

- 4). If a subject refuses to return to clinic during the EOS period, then the visit should be conducted by telephone where appropriate. Refer to the Site Operations Manual for further details regarding scheduling of clinic EOS contacts.
3. **Correct text to be consistent regarding use of telephone and clinic visits to follow subjects who permanently discontinue IP prior to the end of the study.**
- Rationale:**
Provide consistency within protocol.

Section 3.1 (Treatment Phase)

Original Text:

Subjects who qualify for the study will be randomized 1:1 to once daily doses of oral Darapladib Enteric Coated Tablets, 160 mg or matching placebo (hereafter referred to as investigational product [IP]) and enter the Treatment Phase. **During the Treatment Phase, subjects will return for scheduled clinic visits at Month 1, Month 3, Month 6 and then every 6 months thereafter for the duration of the study. In addition, scheduled telephone visits will be conducted beginning at Month 9 and then every 6 months thereafter for the duration of the study. If a subject permanently discontinues treatment with IP prior to the end of the study, then the subject must be followed by telephone visits or other means until the end of the study unless consent is withdrawn.**

Revised Text:

Subjects who qualify for the study will be randomized 1:1 to once daily doses of oral Darapladib Enteric Coated Tablets, 160 mg or matching placebo (hereafter referred to as investigational product [IP]) and enter the Treatment Phase. **During the Treatment Phase, subjects will return for scheduled clinic visits at Month 1, Month 3, Month 6 and then every 6 months thereafter for the duration of the study. In addition, scheduled telephone visits will be conducted beginning at Month 9 and then every 6 months thereafter for the duration of the study. If a subject permanently discontinues treatment with IP prior to the end of the study, then the subject must be followed by telephone visits, in clinic, or other means until the end of the study unless consent is withdrawn.**

Section 4.4 (Stopping IP Early or Withdrawal from the Study)

Original Text:

Subjects have the right to stop taking IP before the end of the study or withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject may also be asked to stop IP at the investigator's discretion. **In the event that a subject permanently discontinues IP before the end of the study, the investigator should continue to follow the subject by telephone to assess study endpoints including MACE (see Section 6.3). In addition investigator should continue to report SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (see Section 6.4.6).**

Subjects who wish to permanently discontinue IP prior to the end of the study but continue in the study will be asked to return for an Early Withdrawal Visit as soon as possible. They will be encouraged to continue taking IP until the day before this visit. If they do not wish to continue taking IP until the day before the Early Withdrawal Visit, or if they cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance). **After the Follow-up Visit, telephone visits will be used in place of scheduled clinic visits to maintain contact with the subject until the end of the study.**

Revised Text:

Subjects have the right to stop taking IP before the end of the study or withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject may also be asked to stop IP at the investigator's discretion. **In the event that a subject permanently discontinues IP before the end of the study, the investigator should continue to follow the subject by telephone or in clinic to assess study endpoints including MACE (see Section 6.3). In addition investigator should continue to report SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (see Section 6.4.6).**

Subjects who wish to permanently discontinue IP prior to the end of the study but continue in the study will be asked to return for an Early Withdrawal Visit as soon as possible. They will be encouraged to continue taking IP until the day before this visit. If they do not wish to continue taking IP until the day before the Early Withdrawal Visit, or if they cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance). **After the Follow-up Visit, telephone visits will be used in place of scheduled clinic visits to maintain contact with the subject until the end of the study. Note: All subjects will be asked to return to the clinic during the EOS period for a final study contact (see Section 3.1). Assessments required for Telephone Visits may be performed in the clinic.**

4. Clarify data collection for subjects who have discontinued IP and are in post-IP follow-up.

Rationale:

Subjects who have discontinued IP and have completed the follow-up visit continue to be followed for study endpoints and other safety data. This section clarifies data

collected for these subjects and when these subjects have completed the study. A new Time and Events table is added to make the Time and Events tables consistent with post-IP follow-up and to stress the importance of a clinic visit at the end of the study.

Section 4.4**Original Text:****Data Collection for Subjects Who Decide to Stop Taking IP before the End of the Study**

Every effort should be made to continue to follow subjects through the end of the study as these subjects will be included in the analyses of time to clinical events. Telephone visits or clinic visits should be used to follow subjects who permanently discontinue IP. These telephone calls or visits should be performed according to the original visit schedule. However, if the subject refuses regular follow-up by phone or in clinic, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable. If the subject declines all further contact with study personnel, subjects should be asked if they will allow follow-up for events through a family or friend contact, through their local physician or through medical records.

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (See Section 6.4.6). **NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of the study.**

Revised Text:**Data Collection for Subjects Who Decide to Stop Taking IP before the End of the Study (i.e., post-IP phone/clinic follow-up)**

Every effort should be made to continue to follow subjects through the end of the study as these subjects will be included in the analyses of time to clinical events. Telephone visits or clinic visits should be used to follow subjects who permanently discontinue IP. These telephone calls or visits should be performed according to the original visit schedule. However, if the subject refuses regular follow-up by phone or in clinic, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable (see Table 4). If the subject declines all further contact with study personnel, subjects should be asked if they will allow follow-up for events through a family or friend contact, through their local physician or through medical records.

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication (See Section 6.4.6) as well as AEs/SAEs of cancer and GI polyps/neoplasms (See Section 6.4.9) should also be reported. **NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of**

the study.

Add Table 4 - Time and Events Table – Assessments for Subjects Who Permanently Discontinue IP Prior to the End of the Study (*It is preferred that these assessments be conducted every 3 months. However, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable. See Section 4.4.)*

Procedures	Phone/Clinic Visit	EOS Clinic Visit ¹
Assessment of MACE and other study endpoints	x	x
SAEs which are assessed as related to Investigational Product (IP), related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication (see Section 6.4.6.)	x	x
Events of cancer and GI polyps/neoplasms (see Section 6.4.9.)	x	x
Vital Signs		x

1. Every effort should be made to conduct the last visit in the clinic during the EOS period (see Section 3.1.). If subjects are unable to return to the clinic a phone contact is allowed.

5. Allow a subject who met liver chemistry stopping criteria to restart IP if liver chemistries have improved to within the normal range, even if >1.5 x Baseline.

Rationale:

Subjects with Baseline liver chemistries near the lower limit of normal may have liver chemistries within the normal range, even if >1.5 x Baseline. This change will allow subjects who met liver chemistry stopping criteria to restart IP if liver chemistries have improved to within the normal range, even if >1.5 x Baseline.

Section 6.4.1.1.

Original Text:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to within 1.5 x baseline and ALT<3xULN.

Revised Text:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to a) within the normal range OR b) ≤1.5x baseline and ALT<3xULN.

Appendix 10 (1st paragraph)

Original Text:

In Phase III-IV, investigational product (IP) restart may be considered for liver safety events with a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to within 1.5x baseline and ALT<3xULN.

Revised Text:

In Phase III-IV, investigational product (IP) restart may be considered for liver safety events with a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to a) within the normal range OR b) $\leq 1.5x$ baseline and $\text{ALT} < 3x\text{ULN}$.

Appendix 10 (Table)**Original Table:**

Checklist for Phase III Investigational Product (IP) restart after well-explained liver injury (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), improving to liver chemistries $\leq 1.5x$ baseline and $\text{ALT} < 3x\text{ULN}$.		
Do not restart if any of the following questions are answered YES	Yes	No
Currently, is $\text{ALT} \geq 3x\text{ULN}$ or are liver chemistries $> 1.5 \times$ Baseline?		
Were any of the following risk factors present at initial liver injury?:		
<ul style="list-style-type: none"> • rash, eosinophilia, or hypersensitivity • drug-induced (IP or non-IP) liver injury • alcoholic hepatitis (e.g., $\text{AST} > \text{ALT}$, typically $< 10x\text{ULN}$) 		

Revised Table:

Checklist for Phase III Investigational Product (IP) restart after well-explained liver injury (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), improving to liver chemistries a) within the normal range OR b) $\leq 1.5x$ baseline and $\text{ALT} < 3 \times \text{ULN}$.		
Do not restart if BOTH of the following questions are answered NO	Yes	No
Currently, are liver chemistries within the normal range?		
Currently, are liver chemistries $\leq 1.5x$ baseline <u>and</u> $\text{ALT} < 3 \times \text{ULN}$?		
Do not restart if any of the following questions are answered YES	Yes	No
Were any of the following risk factors present at initial liver injury?:		
• rash, eosinophilia, or hypersensitivity		
• drug-induced (IP or non-IP) liver injury		
• alcoholic hepatitis (e.g., AST>ALT, typically $< 10 \times \text{ULN}$)		

6. Clarify completion of Follow-up checklist for subjects who withdrew consent for participation in the study.

Rationale:

Clarifies that the withdrawal of consent checklist with follow-up options should be completed for all randomized subjects who withdraw consent.

Section 4.4**Original Text:**

Prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, follow-up through a local physician or through medical records. Follow-up options will be summarized on a withdrawal of consent checklist that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study.

Revised Text:

Prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, follow-up through a local physician or through medical records. Follow-up options will be summarized on a withdrawal of consent checklist that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study. The checklist needs to be completed for all randomized subjects who have withdrawn consent, even for those who withdrew prior to this amendment (Amendment 3).

Amendment 2 – Summary of Changes and Rationale

This is a global amendment and is applicable to all study sites.

The primary intent of this amendment is to allow the Follow-up visit to be conducted by telephone in subjects who meet pre-defined criteria. This change will allow collection of study endpoints/safety data in subjects who may not be able to attend a Follow-up clinic visit.

Additional changes are summarized below.

- **Replace Dr. Patrick Vallance on sponsor signatory and sponsor information pages.**
Dr. Vallance is no longer directly leading the darapladib development.
- **Update List of Abbreviations and correct format errors.**
These changes were made to make the protocol compliant with current GSK protocol guidelines.
- **Revise text regarding scheduling of the End of Treatment visit.**
It is recognized that sites with the most subjects may need more than 4 weeks to schedule all visits. This change is intended to accommodate these schedules in order to maximize follow-up at all sites.
- **Clarify that publically available information may be used to report endpoints/survival status in subjects who withdraw consent to participate in the study.**
This change will allow more comprehensive collection of study endpoints.
- **Remove requirement for investigators to contact the sponsor prior to restarting IP in subjects who have been off IP for more than 1 month.**
The protocol ONLY required the investigator to contact the sponsor prior to restarting IP if the investigator initiated the dosing interruption. It was not required if the subject stopped dosing without the investigator's knowledge.
- **Provide guidance to investigational sites regarding recording the non-adjudicated endpoint “hospitalization for non-coronary ischemic event” in Section 6.3.3.**
This guidance is added to the protocol for clarity.
- **Edit text in Section 6.4.1 (Liver chemistry stopping and follow-up criteria) for improved consistency with algorithm in Appendix 7 (Liver Chemistry Stopping and Follow-up Criteria).**
This change addresses minor inconsistencies between the text in Section 6.4.1 and the flow chart in Appendix 7.
- **Edit text in Section 6.4.3 (Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs) to clarify definition of Hy's law.**
The definition of Hy's law does not include INR.
- **Allow restarting of IP in certain subjects who met liver stopping criteria.**
The current protocol prevents any subject who meets liver chemistry stopping

criteria from ever restarting IP regardless of the presumed reason for the liver chemistry elevation. This change allows **restarting of IP in some subjects**.

List of Protocol Changes with Rationale for Each

1. **Allow the Follow-up visit to be conducted by telephone in subjects who meet pre-defined criteria**

Rationale:

This change will allow collection of study endpoints/safety data in subjects who may not be able to attend a Follow-up clinic visit.

- a. **Section 3.1 (Follow-up Phase)**

Original Text:

The Follow-up Phase begins the day after the final dose of IP.

At the end of the study, a Follow-up Visit will be scheduled to occur 35 ± 7 days after the final dose of IP. If all AEs and serious adverse events (SAEs) have resolved at the time of the Follow-up Visit, no further AE data will be collected. In general, unless the investigator and sponsor discuss an alternative, ongoing AE and SAE data will be collected up to 35 days after the last dose of IP or until the Follow-up Visit, whichever is longer, after which no further data will be collected. Before scheduling any additional clinic visits after the Follow-up Visit, the investigator should first discuss the situation with the sponsor.

NOTE: Subjects who permanently discontinue IP prior to the end of the study should have a Follow-up Visit scheduled to occur 35 ± 7 days after the final dose of IP, but will be followed for clinical outcomes until study termination, unless the subject withdraws consent for any further study-related contact. Additional information regarding vital statistics will be collected if it is available to the public. See Section 4.4, Stopping IP Early or Withdrawal from the Study, for more information.

Revised Text:

The Follow-up Phase begins the day after the final dose of IP.

At the end of the study, a Follow-up Visit will be scheduled to occur 35 ± 7 days after the final dose of IP. If all AEs and serious adverse events (SAEs) have resolved at the time of the Follow-up Visit, no further AE data will be collected. In general, unless the investigator and sponsor discuss an alternative, ongoing AE and SAE data will be collected up to 35 days after the last dose of IP or until the Follow-up Visit, whichever is longer, after which no further data will be collected. Before scheduling any additional clinic visits after the Follow-up Visit, the investigator should first discuss the situation with the sponsor.

The Follow-up visit may be conducted by telephone if the subject has completed an ‘in-clinic’ EOT/Early Withdrawal (EW) visit and has no unresolved or new safety concerns present at the EOT/EW visit (i.e., elevated liver function tests [LFTs], unresolved SAEs or other safety concerns that, in the investigator’s

opinion, requires an in-clinic Follow-up visit).

Subjects with **unresolved or new safety concerns** present at the EOT/EW visit must have an ‘in-clinic’ Follow-up visit. For those subjects unable to participate in an ‘in-clinic’ Follow-up visit (i.e., documented subject refusal, subject hospitalized, etc.), the reason must be documented in the source documentation and a telephone Follow-up visit may be conducted.

NOTE: Subjects who permanently discontinue IP prior to the end of the study should have a Follow-up Visit scheduled to occur 35 ± 7 days after the final dose of IP, but will be followed for clinical outcomes until study termination, unless the subject withdraws consent for any further study-related contact. Additional information regarding survival status will be collected if it is available to the public. See Section 4.4, Stopping IP Early or Withdrawal from the Study, for more information.

b. **Table 2 (footnote #3)**

Original Text:

The End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose. If the End-of-Treatment/Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis. **Samples for Lp-PLA2 activity and stored biomarkers are not collected at the Follow-up Visit.**

Revised Text:

The End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose. If the End-of-Treatment/Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis. All subjects are required to complete a Follow-up visit 35 ± 7 days after the final dose of IP. However, the Follow-up Visit may be conducted by telephone under certain circumstances as described in Section 3.1 of the protocol. NOTE: Only assessments required at BOTH the Follow-up visit AND a Telephone visit should be performed for a Telephone Follow-up visit. **Samples for Lp-PLA2 activity and stored biomarkers are not collected at the Follow-up Visit and should not be obtained if the EOT/EW visit is performed more than 24 ± 2 hours after last dose of IP.**

1. **Replace Dr. Patrick Vallance on sponsor signatory and sponsor information pages**

Rationale:

Dr. Vallance is no longer directly leading the darapladib development.

a. **Sponsor Signatory page**

Original Text:

Dr. Patrick Vallance
Head, Medicines Discovery and Development

Revised Text:

Elizabeth Tarka, MD, FACC
Director, Clinical Development

b. **Sponsor Information Page**

Original Text:

Dr Patrick Vallance
Head, Medicines Discovery and Development
980 Great West Road
Brentford
Middlesex TW8 9GS, U.K.
Tel: + 44 208 047 1885

Mary Ann Lukas, MD, FACC
Senior Director, Cardiovascular & Metabolic MDC
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200 North 16th Street
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Elizabeth Tarka, MD, FACC
Director, Cardiovascular & Metabolic MDC
GlaxoSmithKline
2301 Renaissance Blvd
RN0410

Revised Text:

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2. Update List of Abbreviations and correct format errors.

Rationale:

These changes were made to make the protocol compliant with current GSK protocol guidelines.

3. Revise text regarding scheduling of the End of Treatment visit.

Rationale:

It is recognized that sites with the most subjects may need more than 4 weeks to schedule all visits. This change is intended to accommodate these schedules in order to maximize follow-up at all sites.

Section 3.1 (End-of-Treatment)

Original Text:

When it is projected that approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred, the investigators will be notified to contact all subjects to schedule an End-of-Treatment Visit to take place within 4 weeks of notification of the investigator. Investigators will be strongly encouraged to schedule visits sooner than 4 weeks if possible. Subjects will be instructed to continue taking IP as usual until the day before this visit occurs. Subjects will return all remaining IP at this visit.

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance).

Revised Text:

When it is projected that approximately 1500 reports of first occurrence of MACE (primary endpoint) have occurred, the sponsor will notify investigators to begin scheduling end of study contacts (i.e. EOT visits for subjects who have not discontinued IP, final telephone calls for subjects in phone or third party Follow-up, and survival status searches for subjects who have withdrawn from the study or are lost to Follow-up) for all their study subjects in accordance with a pre-defined study close-out period. Subjects will be instructed to continue taking IP as usual until the day before this visit occurs. Subjects will return all remaining IP at this visit.

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed in clinic at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA2 activity and stored biomarkers should not be collected in this instance).

4. **Clarify that publically available information may be used to report endpoints/survival status in subjects who withdraw consent to participate in the study.**

Rationale:

This change will allow more comprehensive collection of study endpoints.

Section 4.4 (Data Collection Following Withdrawal of Consent For Further Participation In The Study)

Original Text:

In subjects withdrawing consent to provide any additional information, no further study visits or study-related telephone contacts can be conducted. Additional information regarding vital statistics will be collected if it is available to the public.

Revised Text:

In subjects withdrawing consent to provide any additional information, no further study visits or study-related telephone contacts can be conducted. Additional information regarding survival status will be collected if it is available to the public.

For any subject who is found to be deceased following survival status searches, the death must be recorded on the death endpoint form and on the SAE-EP page. Wherever possible, cause of death should be provided if available in the public domain.

Any deaths reported through the survival status search must also be submitted as a study endpoint to be adjudicated by the Clinical Endpoint Committee. When submitting source information to the Clinical Endpoint Committee, investigators need to use their judgment to ensure only information available in the public domain is provided.

5. **Remove requirement for investigators to contact the sponsor prior to restarting IP in subjects who have been off IP for more than 1 month.**

Rationale:

The protocol ONLY required the investigator to contact the sponsor prior to restarting IP if the investigator initiated the dosing interruption. It was not required if the subject stopped dosing without the investigator's knowledge.

Original Text:

Investigators may temporarily suspend IP dosing at their discretion although the time off IP should be minimized. If the total time off IP between visits is more than 1

month (or anticipated to be more than 1 month), the investigator should contact the medical monitor or TIMI medical hotline to review medical reasons and steps undertaken to assure patient's continued adherence to IP. The exact dates of investigator-approved stopping and re-starting IP should be recorded in the eCRF. This investigator-initiated suspension of IP will not count toward overall compliance.

Revised Text:

Investigators may temporarily suspend IP dosing at their discretion although the time off IP should be minimized. If the total time off IP between visits is more than 1 month (or anticipated to be more than 1 month), it is recommended that the investigator contact the medical monitor or TIMI medical hotline.

The purpose of this contact is:

- **Awareness by the sponsor and TIMI of which subjects are requiring temporary IP suspension, for what reasons and for what duration.**
- **Provide opportunity if required for discussion and agreement of strategies and appropriateness of restarting IP, and/or of agreement when the subject should be considered permanently withdrawn from IP.**

6. **Provide guidance to investigational sites regarding recording the non-adjudicated endpoint “hospitalization for non-coronary ischemic event” in Section 6.3.3.**

Rationale:

This guidance is added to the protocol for clarity.

Original Text:

Total vascular events that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary [excluding PCI planned prior to randomization but performed after randomization]), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo.

Revised Text:

Total vascular events that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary [excluding PCI planned prior to randomization but performed after randomization]), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo. NOTE: Unplanned hospitalization for a new peripheral arterial ischemic event should be reported as the endpoint “Hospitalization for a non-coronary ischemic event”. This includes patients with acute limb or visceral ischemia, including acute ischemia caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure.

7. **Edit text in Section 6.4.1 (Liver chemistry stopping and follow-up criteria) for improved consistency with algorithm in Appendix 7 (Liver Chemistry Stopping and Follow-up Criteria).**

Rationale:

This change addresses minor inconsistencies between the text in Section 6.4.1 and the flow chart in Appendix 7.

Section 6.4.1**Original Text**

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below:

1. ALT \geq 3xULN and bilirubin \geq 2xULN ($>35\%$ direct bilirubin).

2. ALT \geq 8xULN.

3. ALT \geq 5xULN but $<$ 8xULN persists for \geq 2 weeks

4. ALT \geq 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.

5. ALT \geq 5xULN but $<$ 8xULN and cannot be monitored for $>$ 2 weeks.

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately withdraw investigational product.**
- Report the event to GSK or the TIMI medical hotline 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 \geq 3xULN and bilirubin \geq 2xULN ($>35\%$ direct), termed 'Hy's Law', must be reported as an SAE.

Revised Text:

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below:

1. ALT \geq 3xULN and total bilirubin \geq 2xULN ($>35\%$ direct bilirubin) OR (ALT \geq 3xULN and INR $>$ 1.5, if international normalized ratio [INR] measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: 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 \geq 8xULN.
3. ALT \geq 5xULN but <8 xULN persists for \geq 2 weeks
4. ALT \geq 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for \geq 2 weeks.

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately withdraw investigational product.**
- Report the event to GSK or the TIMI medical hotline 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 \geq 3xULN and total bilirubin \geq 2xULN ($>35\%$ direct), termed 'Hy's Law', OR (ALT \geq 3xULN and INR >1.5 , if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants) **must be reported as an SAE.**

8. Edit text in Section 6.4.3 (Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs) to clarify definition of Hy's law

Rationale:

The definition of Hy's law does not include INR.

Original Text:

All events of possible drug-induced liver injury with hyperbilirubinemia (defined as ALT \geq 3xULN **plus** bilirubin \geq 2xULN [and/or INR >1.5 **if not on anticoagulation therapy**]) or Hy's Law events, require immediate study drug cessation and reporting as an SAE.

Revised Text:

All events of possible drug-induced liver injury with hyperbilirubinemia (defined as ALT \geq 3xULN **plus** total bilirubin \geq 2xULN, or Hy's Law events, OR [ALT \geq 3xULN and INR >1.5 **if not on anticoagulation therapy**]) require immediate study drug cessation and reporting as an SAE.

9. Allow restarting of IP in subjects who meet liver stopping Criteria.

Rationale:

The current protocol prevents any subject who meets liver chemistry stopping criteria from ever restarting IP regardless of the presumed reason for the liver chemistry elevation. This change allows **restarting of IP in some subjects**.

NEW AND REVISED TEXT

Section 6.4.1.

CHANGE “• Do not re-challenge with IP.” **TO** “• Do not restart investigational product unless approval is granted by GSK Medical Governance (details for

restarting investigational product are described in Section 6.4.1.1 and Appendix 10.”

**ADD SECTION 6.4.1.1. (Restarting Investigational Product)
IP Restart Following Transient Resolving Liver Events Not Associated with
Drug-induced (IP or non-IP) Liver Injury**

Approval by GSK for IP restart can be considered where:

- The local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) has approved that **subjects at the site can be considered for restart of IP** as described in Appendix 10.
- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to within 1.5x baseline and ALT<3xULN.
- GSK will inform the investigator of the decision to restart or not restart IP.
- If restart of IP is approved by GSK, the subject must provide signed informed consent specifically for the restart, which clearly describes risks and possible benefits of IP re-start. Documentation of informed consent must be recorded in the study chart.
- Subjects approved by GSK for restarting IP must return to the clinic within one month after IP re-start for repeat liver chemistries. If these are elevated but not meeting protocol-defined liver stopping criteria as per Section 6.4.1 of the protocol, they should be repeated monthly, or sooner in accordance with investigator judgment, until no longer elevated or increasing. If protocol defined stopping criteria for liver chemistry elevations are met after restarting IP, IP must be permanently stopped and/or subjects must be followed as per Section 6.4.1.

Appendix 7

CHANGE “Subject continues in the study after liver chemistry monitoring complete + do not re-challenge with IP” **TO** “Subject continues in the study after liver chemistry monitoring complete + do not re-challenge with IP without permission from GSK (see Appendix 10)”

ADD APPENDIX 10 (Liver Safety Investigational Product Restart Guidelines)

In Phase III-IV, investigational product (IP) restart may be considered for liver safety events with a clear underlying cause (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), if not associated with drug-induced (IP or non-IP) liver injury, alcoholic hepatitis, rash, eosinophilia or hypersensitivity, when liver chemistries have improved to within 1.5x baseline and ALT<3xULN.

Investigational Product (IP) Restart Guidelines

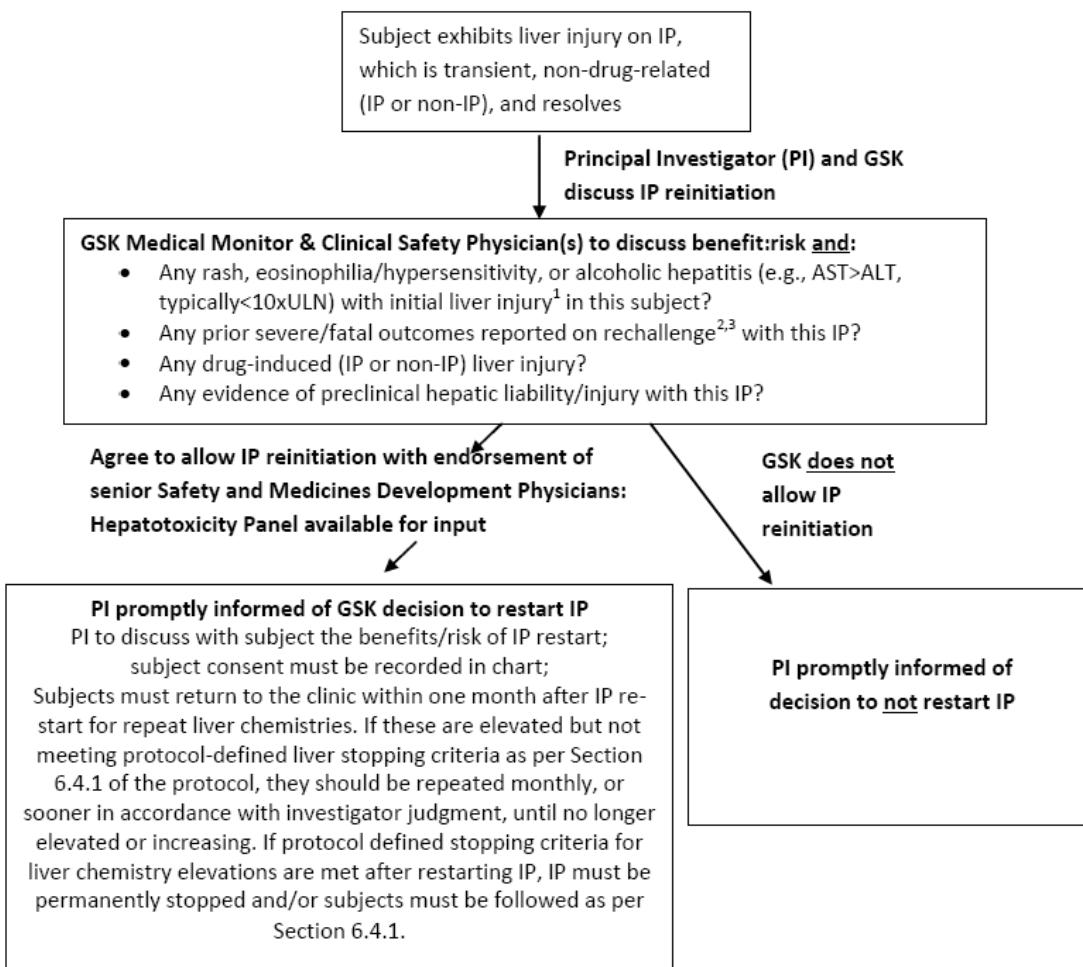
GSK Decision Process for IP Restart Approval or Disapproval (also see Figure 3)

- Principal Investigator (PI) and GSK discuss IP re-initiation for a subject who exhibits liver chemistry elevation meeting IP stopping criteria, which is transient, non-drug-related (IP or non-IP), and resolves.
- GSK Medical Monitor & Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (See Table below).

Checklist for Phase III Investigational Product (IP) restart after well-explained liver injury (e.g., biliary obstruction, pancreatic events, hypotension, CHF, acute viral hepatitis), improving to liver chemistries $\leq 1.5 \times$ baseline and ALT $< 3 \times$ ULN.		
Do not restart if any of the following questions are answered YES	Yes	No
Currently, is ALT $\geq 3 \times$ ULN or are liver chemistries $> 1.5 \times$ Baseline?		
Were any of the following risk factors present at initial liver injury?:		
• rash, eosinophilia, or hypersensitivity		
• drug-induced (IP or non-IP) liver injury		
• alcoholic hepatitis (e.g., AST $>$ ALT, typically $< 10 \times$ ULN)		

*Principal Investigator (PI) Actions

- PI must discuss the benefits and risks of IP re-initiation with the subject.
- The subject must provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Subjects must return to the clinic within one month after IP re-start for repeat liver chemistries. If these are elevated but not meeting protocol-defined liver stopping criteria as per Section 6.4.1 of the protocol, they should be repeated monthly, or sooner in accordance with investigator judgment, until no longer elevated or increasing. If protocol defined stopping criteria for liver chemistry elevations are met after restarting IP, IP must be permanently stopped and/or subjects must be followed as per Section 6.4.1.
- The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.
- GSK to be notified of any adverse or serious adverse events, as per Section 6.4.2 and Section 6.4.3.

Figure 3: GSK Process for Investigational Product (IP) Restart Approvals

¹Andrade RJ. Expert Opin Drug Safe 2009;8:709-714 ²Papay JL. Regul Tox Pharm 2009;54:84-90 ³Hunt CM. Hepatol 2010;52:2116-2222

Amendment 1 – Summary of Changes and Rationale (30-NOV-2010)

This is a global amendment and is applicable to all study sites. The primary intent of this amendment is to revise certain inclusion and exclusion criteria.

The following changes are considered to be substantial changes:

- In exclusion criterion 4 and footnote 10, the definition of liver disease is revised, AST is removed from the list of required liver function tests, and subjects with chronic stable hepatitis may be enrolled under certain circumstances.
- In exclusion criterion 14, the plasma Lp-PLA₂ activity threshold for excluding subjects of Japanese, Chinese or Korean ancestry is revised from ≤ 10 to ≤ 20.0 nmol/min/mL.

The following changes are not considered to substantially affect the overall benefit-risk of the subjects participating in the study, the scientific value of the study, or the conduct or management of the study:

- The Greenford address is deleted from the Sponsor Information Page because this site has closed.
- The address and phone number for Dr. Patrick Vallance are updated on the Sponsor Information Page.
- The Harlow address and phone number are updated on the Sponsor Information Page because this site has partially closed.
- For the composite measure of total coronary events, it is clarified that a PCI planned prior to randomization but performed after randomization will not count towards the composite measure of total coronary events.
- The reference for the guidelines for the management of patients with STEMI is updated in accordance with the latest guidelines issued by the American College of Cardiology/American Heart Association.
- For eligibility assessments, it is revised that local laboratory values obtained from samples collected after the subject signs the ICF may be used; also, it is clarified that the central laboratory must be used beginning with the Baseline Visit.
- In inclusion criterion 2, it is specified that, in Taiwan, subjects must be at least 20 years of age at randomization due to a local requirement.
- Inclusion criterion 3c is revised to allow a diagnostic elevation in creatine kinase to be included in the definition of STEMI.
- This statement is deleted from footnote 6: “Significant renal dysfunction refers to reduced eGFR based on serum creatinine prior to cardiac catheterization or PCI based on local laboratory values.”
- In inclusion criterion 4e, it is clarified that, to meet the definition of polyvascular disease, arterial disease must be manifested as at least cerebrovascular disease or peripheral arterial disease, but not necessarily both, in addition to coronary artery disease manifested by ACS.

- In exclusion criterion 2, it is clarified that “absence of obstructive coronary artery disease” would not include the scenario in which all lesions are successfully treated by PCI.
- In footnote 12 for exclusion criterion 7, when measuring BP, a mean of 3 measurements is preferred but no longer mandated.
- The list of examples of strong CYP3A4 inhibitors is updated.
- In exclusion criterion 12, the text is revised to clarify that a subject with alcohol or drug abuse within the past 6 months must not be enrolled regardless of the investigator’s assessment regarding the subject’s ability to comply with the study requirements.
- In footnote 14 for exclusion criterion 14, the reference for effect of the 279F variant on Lp-PLA₂ activity is updated.
- Less frequent telephone follow-up in subjects who discontinue IP prior to the end of the study is now allowed.
- It is clarified that clinic visits may be used to collect data specified for telephone visits if desired.
- A new paragraph is added to emphasize the need to review and document all options for subject follow-up before confirming that the subject has withdrawn consent.
- Among the possible reasons for discontinuation of IP, “Sponsor terminated study treatment” is added.
- The description of the randomization number is corrected from a 5- to a 6-digit number.
- It is clarified that the first dose of IP should be taken on the day of randomization.
- Expedited SAE reports sent to clinical investigators no longer identify the subject’s treatment assignment.
- In the Time and Events Table 1, it is specified that the Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization.
- In the Time and Events Table 2, the modified Rankin Scale and pregnancy test are now optional for unscheduled visits.
- In the Time and Events Table 2, the IVRS call is removed from unscheduled visits.
- In the Time and Events Table 2, footnote 3, it is noted that the End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within the window for collecting the trough Lp-PLA₂ activity sample (24 ± 2 hours after the final IP dose) or earlier, and that samples for Lp-PLA₂ activity and stored biomarkers are not collected at the Follow-up Visit.
- In the Time and Events Table 2, footnote 4, smoking status was included in error and is now deleted from the list of post-randomization full physical exam assessments.
- “All coronary revascularization procedures” is added as an “other” endpoint.

- The phrase “the first occurrence of” is deleted from the “other” endpoint of total vascular events.
- The list of “Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs” is revised to include all non-fatal strokes.
- It is clarified that the modified Rankin scale is performed in all subjects regardless of stroke history.
- The statement that the treatment effect will be assessed at a nominal 0.05 significance level for the integrated efficacy analyses is deleted.

List of Protocol Changes with Rationale for Each

1. Sponsor Information Page

Delete the Greenford address, update the address and phone number for Dr. Patrick Vallance, and update the Harlow address and phone number.

Rationale:

The Greenford site has closed and the Harlow site has partially closed.

2. Protocol Summary

Original Text:

The composite measure of **total coronary events** that include CHD death, non-fatal MI, hospitalization for UA, or any coronary revascularization procedure.

Revised Text:

The composite measure of **total coronary events** that include CHD death, non-fatal MI, hospitalization for UA, or any coronary revascularization procedure (excluding percutaneous coronary intervention [PCI] planned prior to randomization but performed after randomization).

Rationale:

It is clarified that a PCI planned prior to randomization but performed after randomization will not count towards the composite measure of total coronary events.

3. Section 3.1: Study Design

Original Text:

During the Screening Phase, the subject should be started and/or continued on the standard of care for ACS during in-hospital treatment and after hospital discharge according to local professional guidelines for secondary prevention patient population [Smith, 2006; Anderson, 2007; Antman, 2008; Bassand, 2007; Van de Werf, 2008].

Revised Text:

During the Screening Phase, the subject should be started and/or continued on the standard of care for ACS during in-hospital treatment and after hospital discharge according to local professional guidelines for secondary prevention patient population [Smith, 2006; Anderson, 2007; Kushner, 2009; Bassand, 2007; Van de Werf, 2008].

Rationale:

The American College of Cardiology/American Heart Association has updated their guidelines for the management of patients with STEMI. In accordance, this reference is updated from Antman, 2008 to Kushner, 2009.

4. Section 3.1: Study Design**Original Text:**

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 were done before randomization and the subject has signed the ICF, the results of these procedures may be used to complete the screening log eCRF.

Revised Text:

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 were done before randomization, the results of these procedures may be used to complete the screening log eCRF. (NOTE: The Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization.)

Rationale:

It is not required for the subject to sign the ICF before using results from study qualification procedures to complete the screening log eCRF if these procedures were performed as part of routine care. It is also revised that the Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization. The goal of these baseline assessments is to document the subject's status as close as possible to randomization.

5. Section 3.1: Study Design**Original Text:**

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory.

Revised Text:

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **NOTE: For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization \leq 30 days following hospitalization for ACS.**

Rationale:

This section is revised to allow the use of local laboratory values from samples obtained after the subject signs the ICF to assess eligibility, when necessary due to time constraints.

6. Section 3.1: Study Design**Original Text:**

Liver function assessments (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin)

Revised Text:

Liver function assessments (alanine aminotransferase [ALT], alkaline phosphatase, bilirubin)

Rationale:

AST is removed from the list of required liver function assessments during the screening phase to assess eligibility because the ALT assessment is much more specific for evaluating liver function abnormalities. Alkaline phosphatase had been omitted from this section in error.

7. Section 3.1: Study Design**Original Text:**

Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the laboratory values were obtained \leq 8 weeks before randomization and prior to signing the ICF. Alternatively, the central laboratory may be utilized for the above study qualification laboratory tests. After the subject signs the ICF, the central laboratory must be used for all protocol-specified study qualification laboratory tests.

Revised Text:

Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the laboratory values were obtained \leq 8 weeks before randomization. Alternatively, the central laboratory may be utilized for the above study qualification laboratory tests. Beginning with the Baseline Visit, the central laboratory must be used for all protocol-specified laboratory tests.

Rationale:

This paragraph is revised to allow the use of local laboratory values from samples obtained after the subject signs the ICF to assess eligibility, and to note that the central laboratory must be used beginning with the Baseline Visit.

8. Section 3.1: Study Design**Original Text:**

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, the End-of-Treatment Visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP

Revised Text:

NOTE: The subject will be encouraged to continue taking IP until the day before the End-of-Treatment Visit. If the subject does not wish to continue taking IP until the End-of-Treatment Visit, or if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the End-of-Treatment Visit will not be done and the

subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the End-of-Treatment Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance).

Rationale:

This paragraph is edited to emphasize the End-of-Treatment Visit window and the assessments that must be performed at the Follow-up Visit if the End-of-Treatment Visit is missed.

9. Section 4.2: Inclusion Criteria**Original Text:**

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory.

Revised Text:

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **For samples collected to assess study qualification laboratory values *after* the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS.**

Rationale:

This statement is revised to allow the use of local laboratory values obtained after the subject signs the ICF to assess eligibility, when necessary due to time constraints.

10. Section 4.2: Inclusion Criterion 2**Original Text:**

Male or female aged at least 18 years, inclusive, at randomization. Female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy (refer to Appendix 1).²⁹ 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.

Revised Text:

Male or female aged at least 18 years, inclusive, at randomization. Female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy (refer to Appendix 1).²⁹ 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. In Taiwan, subjects must be aged at least 20 years, inclusive, at randomization.

Rationale:

It is specified that, in Taiwan, subjects must be at least 20 years of age at randomization due to a local requirement.

11. Section 4.2: Inclusion Criterion 3c**Original Text:**

ST segment elevation MI (STEMI) is defined as prolonged symptoms of ischemic chest discomfort (or equivalent) at rest (with at least 1 episode lasting >20 min) and new or presumably new electrocardiographic changes (persistent ST segment elevation ≥ 0.1 mV in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads or new LBBB) that are accompanied by a diagnostic elevation in cardiac biomarkers (serum troponin I or T, or creatine kinase-MB) above the upper limit of normal.

Revised Text:

ST segment elevation MI (STEMI) is defined as prolonged symptoms of ischemic chest discomfort (or equivalent) at rest (with at least 1 episode lasting >20 min) and new or presumably new electrocardiographic changes (persistent ST segment elevation ≥ 0.1 mV in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads or new LBBB) that are accompanied by a diagnostic elevation in cardiac biomarkers (serum troponin I or T, creatine kinase or creatine kinase-MB) above the upper limit of normal.

Rationale:

The inclusion criterion is revised to allow a diagnostic elevation in creatine kinase to be included in the definition of STEMI.

12. Section 4.2: Inclusion Criterion 4d, footnote 6**Original Text:**

⁶**Note:** Significant renal dysfunction refers to reduced eGFR based on serum creatinine prior to cardiac catheterization or PCI based on local laboratory values. Dye-induced nephropathy following cardiac catheterization or PCI during index hospitalization for ACS does not constitute chronic kidney disease.

Revised Text:

⁶**Note:** Dye-induced nephropathy following cardiac catheterization or PCI during index hospitalization for ACS does not constitute chronic kidney disease.

Rationale:

This deletion allows for the use of an eGFR value that was obtained following cardiac catheterization or PCI as long as the value is not believed to be explained by a transient drop in the eGFR due to contrast-induced nephropathy.

13. Section 4.2: Inclusion Criterion 4e**Original Text:**

polyvascular disease manifested as coexistent clinically diagnosed arterial disease in at least 2 arterial territories:

Revised Text:

polyvascular disease manifested in this ACS population as coexistent clinically diagnosed arterial disease in at least 1 peripheral arterial territory, defined as:

Rationale:

The revised text clarifies that, to meet the definition of polyvascular disease, arterial

disease must be manifested as at least cerebrovascular disease or peripheral arterial disease, but not necessarily both, in addition to coronary artery disease manifested by ACS.

14. Section 4.3: Exclusion Criteria

Original Text

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory

Revised Text

If unavailable, then the subject will sign the ICF and sample(s) will be collected and sent to the central laboratory or an accredited local laboratory. **For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS**

Rationale:

This statement is revised to allow the use of local laboratory values obtained from samples collected after the subject signs the ICF to assess eligibility, when necessary due to time constraints.

15. Section 4.3: Exclusion Criterion 2

Original Text:

Absence of obstructive coronary artery disease (i.e., at least one stenosis [$>50\%$] in a major vessel, major branch or bypass graft) based on angiography, if performed, between the time of presentation with ACS and randomization.

Revised Text:

Absence of obstructive coronary artery disease (i.e., at least one stenosis [$>50\%$] in a major vessel, major branch or bypass graft) based on angiography, if performed, between the time of presentation with ACS and randomization. (**NOTE:** If all stenoses are successfully treated by PCI, the patient is still eligible.)

Rationale:

The added note clarifies that “absence of obstructive coronary disease” would not include the scenario in which all lesions are successfully treated by PCI.

16. Section 4.3: Exclusion Criterion 4 and Footnote 10

Original Text:

Current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase $>1.5 \times$ upper limit of normal [ULN]; or ALT or AST $>2.5 \times$ ULN) or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study.¹⁰

¹⁰Note: Isolated AST elevation in patients with acute MI is not considered an exclusion.

Revised Text:

Cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), unstable liver disease (defined by the presence of any of the following felt 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 evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase $>1.5 \times$ upper limit of normal [ULN]; or ALT $>2.5 \times$ ULN) or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study.¹⁰

¹⁰Note: Chronic stable hepatitis B or C are considered an exclusion if there are elevated liver chemistries (elevated ALT, alkaline phosphatase or bilirubin as defined in exclusion criterion 4) or if the subject is receiving (or will receive) significant immunosuppressive agent(s) due to the risk of hepatitis B reactivation.

Rationale:

The revised text updates the definition of liver disease. AST is removed from the list of required liver function assessments during the screening phase to assess eligibility because the ALT assessment is much more specific for evaluating liver function abnormalities. Footnote 10 is revised to note that subjects with chronic stable hepatitis may be eligible for enrollment under certain circumstances.

17. Section 4.3: Exclusion Criterion 7, Footnote 12**Original Text:**

¹²Poorly controlled hypertension refers to either systolic BP >160 mm Hg or diastolic BP >110 mm Hg (mean of 3 measurements according to protocol-specified conditions).

Revised Text:

¹²Poorly controlled hypertension refers to either systolic BP >160 mm Hg or diastolic BP >110 mm Hg (BP should be measured according to protocol-specified conditions; a mean of 3 measurements is preferred but not mandated).

Rationale:

Following the IDMC review of unblinded ambulatory blood pressure monitoring data from the STABILITY trial, the requirement to obtain a mean of 3 BP measurements is removed.

18. Section 4.3: Exclusion Criterion 13, Footnote 13**Original Text:**

¹³ Note: Examples of strong CYP3A4 inhibitors include, but are not limited to the **antiretrovirals** atazanavir, indinavir, nelfinavir, ritonavir, saquinavir; the **macrolide/ketolide antibiotics** clarithromycin, telithromycin, troleandomycin; and the **oral antifungals** ketoconazole, itraconazole. Refer to the SOM for acceptable treatment alternatives. Of note, weaker CYP3A4 inhibitors are allowed, including verapamil, diltiazem, or amiodarone.

Revised Text:

¹³ Note: Examples of strong CYP3A4 inhibitors include, but are not limited to the **antiretrovirals** atazanavir, indinavir, nelfinavir, ritonavir, saquinavir; the

macrolide/ketolide antibiotics clarithromycin, telithromycin, troleandomycin; the **systemic antifungals** ketoconazole, itraconazole, posaconazole, voriconazole; and the **vasopressin receptor antagonist** conivaptan. Refer to the SOM for acceptable treatment alternatives. Of note, weaker CYP3A4 inhibitors are allowed, including verapamil, diltiazem, or amiodarone.

Rationale:

Posaconazole, voriconazole and conivaptan recently have been identified as strong CYP3A4 inhibitors and are included as examples.

19. Section 4.3: Exclusion Criterion 12

Original Text:

Alcohol or drug abuse within the past 6 months, or 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.

Revised Text:

Alcohol or drug abuse within the past 6 months. 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.

Rationale:

The revised text clarifies that a subject with alcohol or drug abuse within the past 6 months must not be enrolled regardless of the investigator's assessment regarding the subject's ability to comply with the study requirements.

20. Section 4.3: Exclusion Criterion 14 and Footnote 14

Original Text:

Subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory prior to randomization. Those with Lp-PLA₂ activity ≤ 10 nmol/min/mL will be excluded from participation in the study.¹⁴

¹⁴ Subjects homozygous for the V279F variant have no circulating levels of Lp-PLA₂ and would not expect to benefit from Lp-PLA₂ lowering therapy. This allele is most common in those of Japanese [Ishihara, 2004], Chinese [Liu, 2006], and Korean [Jang, 2006] ancestry.

Revised Text:

Subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory prior to randomization. Those with Lp-PLA₂ activity ≤ 20.0 nmol/min/mL will be excluded from participation in the study.¹⁴

¹⁴ Subjects homozygous for the 279F variant have no circulating levels of Lp-PLA₂ and would not expect to benefit from Lp-PLA₂ lowering therapy. This allele is most common in those of Japanese, Chinese, and Korean ancestry [Stafforini, 2009].

Rationale:

The original text excluded Japanese, Chinese and Korean subjects with plasma Lp-PLA₂ activity ≤ 10 nmol/min/mL prior to randomization. Recent data from subjects with chronic coronary heart disease in the STABILITY trial suggest that Japanese, Chinese and Korean subjects who are homozygous for the 279F variant may have reported Baseline plasma Lp-PLA₂ activity levels approaching 20.0 nmol/min/mL when measured by the assay used in this study. The revised text excludes Japanese, Chinese and Korean subjects with plasma Lp-PLA₂ activity ≤ 20.0 nmol/min/mL prior to randomization, which should help ensure that Japanese, Chinese and Korean subjects who are homozygous for the 279F variant are not enrolled. The reference for effect of the 279F variant on Lp-PLA₂ activity is updated.

21. Section 4.4: Stopping IP Early or Withdrawal from the Study**Original Text:**

Subjects who wish to permanently discontinue IP prior to the end of the study but continue in the study will be asked to return for an Early Withdrawal Visit as soon as possible. They will be encouraged to continue taking IP until the day before this visit. If they do not wish to continue taking IP until the day before the Early Withdrawal Visit, the Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. **After the Follow-up Visit, telephone visits will be used in place of scheduled clinic visits to maintain contact with the subject until the end of the study.**

Revised Text:

Subjects who wish to permanently discontinue IP prior to the end of the study but continue in the study will be asked to return for an Early Withdrawal Visit as soon as possible. They will be encouraged to continue taking IP until the day before this visit. If they do not wish to continue taking IP until the day before the Early Withdrawal Visit, or if they cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose, the Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit 35 ± 7 days following the final dose of IP. If the Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis (samples for Lp-PLA₂ activity and stored biomarkers should not be collected in this instance). **After the Follow-up Visit, telephone visits will be used in place of scheduled clinic visits to maintain contact with the subject until the end of the study.**

Rationale:

This paragraph is edited to emphasize the Early Withdrawal Visit window and the assessments that must be performed at the Follow-up Visit if the Early Withdrawal Visit is missed.

22. Section 4.4: Stopping IP Early or Withdrawal from the Study

A new subsection is added:

Data Collection for Subjects Who Decide to Stop Taking IP Before the End of the Study

Every effort should be made to continue to follow subjects through the end of the

study as these subjects will be included in the analyses of time to clinical events. Telephone visits or clinic visits should be used to follow subjects who permanently discontinue IP. These telephone calls or visits should be performed according to the original visit schedule. However, if the subject refuses regular follow-up by phone or in clinic, less frequent calls (e.g., every 6 or 12 months) or clinic visits to report events are acceptable. If the subject declines all further contact with study personnel, subjects should be asked if they will allow follow-up for events through a family or friend contact, through their local physician or through medical records.

Study endpoints, especially MACE (See Section 6.3), should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported (See Section 6.4.6). **NOTE: Every effort must be made to obtain survival status for each randomized subject at the end of the study.**

Rationale:

This addition is intended to increase the number of subjects who allow telephone follow-up after discontinuing IP by reducing the number of required phone calls. Subject status for the primary endpoint still will be collected at the end of the study. This addition also clarifies that clinic visits may be used to collect data specified for telephone visits if desired.

23. Section 4.4: Data Collection Following Withdrawal of Consent for Further Participation in the Study

A new paragraph is added:

Prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, follow-up through a local physician or through medical records. Follow-up options will be summarized on a withdrawal of consent checklist that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study.

Rationale:

The added paragraph emphasizes the need to review and document all options for subject follow-up before confirming that the subject has withdrawn consent.

24. Section 4.4: Possible Reasons for Discontinuation of Investigational Product Original Text:

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

- Adverse experience requiring discontinuation including liver chemistry abnormalities (see Section 6.4.1)
- Subject becomes pregnant during the study
- Protocol deviation
- Decision by subject or proxy
- Lost to follow-up

Revised Text:

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

- Adverse experience requiring discontinuation including liver chemistry abnormalities (see Section 6.4.1)
- Subject becomes pregnant during the study
- Protocol deviation
- Decision by subject or proxy
- Sponsor terminated study treatment
- Lost to follow-up

Rationale:

“Sponsor terminated study treatment” is added to the list of possible reasons for discontinuation from IP.

25. Section 5.2: Treatment Assignment**Original Text:**

A 5-digit randomization number which must be recorded in the subject's eCRF.

Revised Text:

A 6-digit randomization number which must be recorded in the subject's eCRF.

Rationale:

The randomization number was incorrectly described as a 5-digit number. The revised text correctly describes the randomization number as a 6-digit number.

26. Section 5.2: Treatment Assignment**Original Text:**

These numbers are unique to each subject and must not be re-assigned.

Revised Text:

These numbers are unique to each subject and must not be re-assigned. The first dose of IP should be taken on the same day as randomization.

Rationale:

It is clarified that IP dosing should begin the same day as randomization.

27. Section 5.3: Blinding**Original Text:**

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Revised Text:

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the

blinded report may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Rationale:

The reports sent to clinical investigators no longer identify the subject's treatment assignment.

28. Section 5.6.2: Prohibited Medications and Non-Drug Therapies**Original Text:**

Examples of strong CYP3A4 inhibitors include, but are not limited to, those listed below.

- The following antiretrovirals: atazanavir, indinavir, nelfinavir, ritonavir, saquinavir
- The following macrolide/ketolide antibiotics: clarithromycin, telithromycin, troleandomycin
- The following antifungals: ketoconazole, itraconazole

Revised Text:

Examples of strong CYP3A4 inhibitors include, but are not limited to, those listed below.

- The following antiretrovirals: atazanavir, indinavir, nelfinavir, ritonavir, saquinavir
- The following macrolide/ketolide antibiotics: clarithromycin, telithromycin, troleandomycin
- The following antifungals: ketoconazole, itraconazole, posaconazole, voriconazole
- The vasopressin receptor antagonist conivaptan

Rationale:

Posaconazole, voriconazole and conivaptan recently have been identified as strong CYP3A4 inhibitors and are included as examples.

29. Section 6: Table 1
Original Text:

Procedures	Screening Phase (begins when written informed consent is obtained and ends at randomization)	Baseline Visit (\leq 30 days after presentation with ACS)
Vital Signs	X	X
Full Physical Examination ²		X
12-lead ECG		X

Revised Text:

Procedures	Screening Phase (begins when written informed consent is obtained and ends at randomization)	Baseline Visit (\leq 30 days after presentation with ACS)
Vital Signs	X	X (within 2 days prior to randomization)
Full Physical Examination ²		X (within 2 days prior to randomization)
12-lead ECG		X (within 2 days prior to randomization)

Rationale:

The revision specifies that the Baseline vital signs, full physical examination and ECG should be performed within 2 days prior to randomization. The goal of these baseline assessments is to document the subject's status as close as possible to randomization.

30. Section 6: Table 1, Footnote 5

Original Text:

Refer to the inclusion/exclusion criteria (Section 4.2 and Section 4.3) for clinical laboratory test results required for study entry (eGFR, total bilirubin, alkaline phosphatase, ALT, AST). Local laboratory values may be used if obtained \leq 8 weeks prior to randomization (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during qualifying hospitalization) and prior to obtaining written informed consent. If unavailable, then obtain written informed consent and send samples to the central laboratory.

Revised Text:

Refer to the inclusion/exclusion criteria (Section 4.2 and Section 4.3) for clinical laboratory test results required for study entry (eGFR, total bilirubin, alkaline phosphatase, ALT). Local laboratory values may be used if obtained \leq 8 weeks prior to randomization (excluding ACS diagnostic biomarkers which must be local laboratory results obtained during qualifying hospitalization). If unavailable, then obtain written informed consent and send samples to the central laboratory or an accredited local laboratory.

Rationale:

AST is removed from the list of required liver function assessments during the screening phase to assess eligibility because the ALT assessment is much more specific for evaluating liver function abnormalities as compared to the value of the AST assessment. The footnote is revised to allow the use of local laboratory values obtained from samples collected after the subject signs the ICF to assess eligibility.

31. Section 6: Table 2

The modified Rankin Scale and pregnancy test are now optional for unscheduled visits.

Rationale:

The modified Rankin Scale and pregnancy test are performed at regularly scheduled visits. This change will make these assessments optional at unscheduled visits unless clinically indicated.

32. Section 6: Table 2

The IVRS call is removed at unscheduled visits.

Rationale:

An IVRS call was erroneously included at the unscheduled visit.

33. Section 6: Table 2, Footnote 3**Original Text:**

If the End-of-Treatment/Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis.

Revised Text:

The End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within 24 ± 2 hours or earlier after the final IP dose. If the End-of-Treatment/Early Withdrawal Visit is missed, the following assessments must be performed at the Follow-up Visit: full physical exam, 12-lead ECG, clinical laboratory tests and urinalysis. **Samples for Lp-PLA₂ activity and stored biomarkers are not collected at the Follow-up Visit.**

Rationale:

The added text clarifies that the End-of-Treatment/Early Withdrawal Visit is not required if the subject cannot visit the clinic within the window for collecting the trough Lp-PLA₂ activity sample (24 ± 2 hours after the final IP dose) or earlier. If this visit is missed, samples for Lp-PLA₂ activity and stored biomarkers are not collected at the Follow-up Visit since any IP-elicited changes would be expected to return toward baseline levels following discontinuation of IP.

34. Section 6: Table 2, Footnote 4**Original Text:**

At minimum: height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, lower and upper extremities exam, and smoking status.

Revised Text:

At minimum: height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, and lower and upper extremities exam.

Rationale:

Smoking status was included in error and is now deleted from the list of post-randomization full physical exam assessments.

35. Section 6.3.2: Secondary Efficacy Endpoints**Original Text:**

The composite measure of total coronary events that include the first occurrence of CHD death, non-fatal MI, hospitalization for unstable angina,²⁰ or any coronary revascularization procedure in darapladib-treated subjects as compared with placebo.

Revised Text:

The composite measure of total coronary events that include the first occurrence of CHD death, non-fatal MI, hospitalization for unstable angina,²⁰ or any coronary revascularization procedure (excluding PCI planned prior to randomization but performed after randomization) in darapladib-treated subjects as compared with placebo.

Rationale:

The revised text clarifies that a coronary revascularization procedure that is planned prior to randomization but is performed after randomization will be excluded from the composite measure of total coronary events.

36. Section 6.3.3: Others

Add endpoint “• All coronary revascularization procedures (excluding PCI planned prior to randomization but performed after randomization).”

Rationale:

“Any coronary revascularization procedure” is currently part of the “total coronary events” composite endpoint. This change allows all coronary revascularization procedures to also be analyzed separately.

37. Section 6.3.3: Others**Original Text:**

Total vascular events that include the first occurrence of any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-coronary), or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo.

Revised Text:

Total vascular events that include any component of MACE, hospitalization for unstable angina or for any other non-coronary ischemic event (e.g., transient ischemic attack or limb ischemia), any revascularization procedure (coronary or non-

coronary [excluding PCI planned prior to randomization but performed after randomization], or limb amputation due to vascular causes in darapladib-treated subjects as compared with placebo.

Rationale:

The phrase “the first occurrence of” is not included in any of the “other” endpoints. This change makes total vascular events consistent with the “other” endpoints. In addition, text is added to clarify that a coronary revascularization procedure that is planned prior to randomization but is performed after randomization will be excluded from the composite measure of total coronary events.

38. Section 6.3.3: Others**Original Text:**

The composite of **total coronary events** (CHD death, non-fatal MI, hospitalization for unstable angina, or any coronary revascularization procedure) in darapladib-treated subjects compared with placebo, **excluding target lesion revascularization** (i.e., restenosis) in subjects treated with PCI prior to randomization.

Revised Text:

The composite of **total coronary events** (CHD death, non-fatal MI, hospitalization for unstable angina, or any coronary revascularization procedure [excluding PCI planned prior to randomization but performed after randomization]) in darapladib-treated subjects compared with placebo, **excluding target lesion revascularization** (i.e., restenosis) in subjects treated with PCI prior to randomization.

Rationale:

The revised text clarifies that a coronary revascularization procedure that is planned prior to randomization but is performed after randomization will be excluded from the composite measure of total coronary events.

39. Section 6.4.4: Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**Original Text:**

- Non-fatal ischemic stroke

Revised Text:

- Non-fatal stroke

Rationale:

Components of the primary efficacy endpoint (MACE) are excluded from expedited reporting to regulatory authorities. Since all non-fatal strokes (i.e., hemorrhagic and ischemic) are included in that endpoint, the revised text indicates that all non-fatal strokes should be excluded from expedited reporting.

40. Section 6.4.8: Other Safety Outcomes**Original Text:**

- **A full physical exam** will assess, at minimum, height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam,

abdominal exam, lower and upper extremities exam, and smoking status.

Revised Text:

- **A full physical exam** will assess, at minimum, height, weight, waist and hip circumference, lung and heart sounds, general appearance, head, hair, skin, nails, eye, ear, nose and sinuses, mouth, pharynx, neck, peripheral vascular exam, abdominal exam, and lower and upper extremities exam.

Rationale:

Smoking status was included in error and is now deleted from the list of post-randomization full physical exam assessments.

41. Section 6.4.8: Other Safety Outcomes**Original Text:**

Modified Rankin Scale: The modified Rankin Scale assesses functional deficits following a stroke (Appendix 5). If possible, the same person should assess the modified Rankin Scale for an individual subject at each visit for that subject.

Revised Text:

Modified Rankin Scale: The modified Rankin Scale assesses functional deficits following a stroke (Appendix 5). The modified Rankin scale will be performed in all subjects regardless of stroke history. If possible, the same person should assess the modified Rankin Scale for an individual subject at each visit for that subject.

Rationale:

The added statement clarifies that the modified Rankin scale is performed on all subjects, including subjects with no history of stroke.

42. Section 6.4.8: Other Safety Outcomes**Original Text:**

During screening, if local laboratory test results required for enrollment (refer to inclusion/exclusion criteria Section 4.2 and Section 4.3) are not available, samples must be collected and sent to the central laboratory for assessment of all of the following: eGFR, total bilirubin, alkaline phosphatase, ALT and AST. In addition, subjects with 2 known birth parents of at least 50% Japanese,

Revised Text:

During screening, if local laboratory test results required for enrollment (refer to inclusion/exclusion criteria Section 4.2 and Section 4.3) are not available, samples must be collected and sent to the central laboratory or an accredited local laboratory for assessment of all of the following: eGFR, total bilirubin, alkaline phosphatase and ALT. **NOTE: For samples collected to assess study qualification laboratory values after the subject signs the ICF, the use of a local laboratory should be limited to circumstances under which central laboratory results may not be available in time to meet the requirement for randomization ≤ 30 days following hospitalization for ACS.**

Rationale:

AST is removed from the list of required liver function assessments during the screening phase to assess eligibility because the ALT assessment is much more specific for evaluating liver function abnormalities as compared to the value of the AST assessment. The text is revised to allow the use of local laboratory values obtained from samples collected after the subject signs the ICF to assess eligibility, when necessary due to time constraints.

43. Section 6.5: Health Economic Outcomes**Original Text:**

All kinds of revascularization procedures and amputation

Revised Text:

All kinds of revascularization procedures and amputation (excluding PCI planned prior to randomization but performed after randomization)

Rationale:

The revised text clarifies that a coronary revascularization procedure that is planned prior to randomization but is performed after randomization will be excluded from the composite measure of total coronary events.

44. Section 8.3.4.1: Efficacy Analyses**Original Text:**

The treatment effect will be assessed at a nominal 0.05 significance level.

Revised Text:

Deleted

Rationale:

Details involving alpha testing thresholds will be described in the Integrated Analysis Plan.

45. Section 10: References

Replace the Antman, 2008 reference with the Kushner, 2009 reference.

Rationale:

The reference for the guidelines for the management of patients with STEMI is updated.

46. Section 10: References

Replace the Ishihara, 2004; Liu, 2006; and Jang, 2006 references with the Stafforini, 2009 reference.

Rationale:

The reference for effect of the 279F variant on Lp-PLA₂ activity is updated.

Division: World Wide Development

Retention Category: GRS019

Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for the SOLID-TIMI 52 Trial (SB-480848/033): A Clinical Outcomes Study of Darapladib versus Placebo in Subjects Following Acute Coronary Syndrome to Compare the Incidence of Major Adverse Cardiovascular Events (MACE)
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Compound Number: SB-480848

Effective Date: 7-Apr-2014

Description: This Reporting and Analysis Plan is intended to describe the statistical analyses required for the SOLID-TIMI 52 Trial (SB-480848/033). The primary objective of this study is to evaluate clinical efficacy of long-term treatment with Darapladib Enteric Coated Tablets, 160 mg (oral once daily dose) as compared to placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events (i.e., CHD death, non-fatal MI, urgent coronary revascularization for myocardial ischemia). The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE) (defined as CV death, non-fatal MI, non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedure; the composite of all-cause mortality, non-fatal MI and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters including relation to and changes in biomarkers of CV risk, health economic outcomes, and adverse events will also be evaluated.

Identifier/Version Number: NA

Subject: atherosclerosis, Lp-PLA₂ inhibitor, acute coronary syndrome, SB480848, darapladib

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ABBREVIATIONS

ACR	Albumin:creatinine Ratio
ACS	Acute Coronary Syndrome
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CEC	Clinical Endpoint Committee
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CNP	Cancer/GI neoplasm/polyp
CPMS	Clinical Pharmacology Modeling & Simulation
CSR	Clinical Study Report
CV	Cardiovascular
DAP	Data Analysis Plan
DBP	Diastolic Blood Pressure
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EC	Enteric Coated
ECG	Electrocardiogram
FDA	Food and Drug Administration
hCG	Human Chorionic Gonadotropin
hsCRP	High Sensitivity C-reactive Protein
HbA ₁ C	Hemoglobin subtype A1c
HBsAg	Heptatitis B Surface Antigen
HDL-C	High-density Lipoprotein Cholesterol
HR	Hazard Ratio
ID	Identification
IDMC	Independent Data Monitoring Committee
IL-6	Interleukin-6
IP	Investigational Product
ITT	Intent-to-treat
LDL-C	Low-density Lipoprotein Cholesterol
Lp-PLA ₂	Lipoprotein-associated Phospholipase A ₂
LYS	Life-Year Saved
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NCI	National Cancer Institute
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention

PP	Per Protocol
PWP	Prentice, Williams, Peterson
RAP	Reporting and Analysis Plan
QALY	Quality-adjusted Life-Year
QTc	Corrected QT
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SDAC	Statistical Data Analysis Center
SOLID-TIMI 52	Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction
STABILITY	STabilisation of Atherosclerotic plaque By Initiation of darapLadIb TherapY
STEMI	ST-segment Elevation Myocardial Infarction
SI	International System of Units
UA	Unstable Angina
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

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1. INTRODUCTION

This Reporting and Analysis Plan (RAP) is intended to describe the statistical analyses required for a Clinical Study Report (CSR) for the **S**tabilization **O**f pLaques us**I**ng **D**arapladib-**T**hrombolysis **I**n Myocardial Infarction 52 [SOLID-TIMI 52] Trial) in investigating the efficacy, safety, and tolerability of darapladib (SB480848), a novel lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor, in subjects following acute coronary syndrome (ACS). This document is based on the protocol and protocol amendments of study SB-480848/033 as listed below:

Final Protocol, Date 08 OCT 2009, [GlaxoSmithKline Document Number [RM 2007/00497/01](#)]

Protocol Amendment 1, Date 30 NOV 2010, [GlaxoSmithKline Document Number [RM 2007/00497/02](#)]

Protocol Amendment 2, Date 26 APR 2012, [GlaxoSmithKline Document Number [RM 2007/00497/03](#)]

Protocol Amendment 3, Date 22 OCT 2012, [GlaxoSmithKline Document Number [RM 2007/00497/04](#)]

Protocol Amendment 4, Date 29 NOV 2012, [GlaxoSmithKline Document Number [RM 2007/00497/05](#)]

Protocol Amendment 5, Date 26 FEB 2014, [GlaxoSmithKline Document Number [RM 2007/00497/06](#)]

Protocol Amendment 5 changed the primary endpoint of the study from major adverse cardiovascular events (MACE) to major coronary events prior to unblinding of treatment assignment. This RAP describes the planned analyses based on this amendment.

The SOLID-TIMI 52 study is the second of two outcome studies investigating darapladib. The first study is STABILITY (STabilisation of Atherosclerotic plaque **B**y Initiation of darap**L**a**I**b Therap**Y**) whose primary objective is to evaluate darapladib versus placebo in a chronic coronary heart disease (CHD) population on the incidence of MACE. More information on the design of the STABILITY trial can be found in the associated protocol and protocol amendments:

Final Protocol, Date 23 SEP 2008, [GlaxoSmithKline Document Number [RM 2007/00471/01](#)]

Protocol Amendment 1, Date 24 AUG 2009, [GlaxoSmithKline Document Number [RM 2007/00471/02](#)]

Protocol Amendment 2, Date 11 FEB 2010, [GlaxoSmithKline Document Number [RM 2007/00471/03](#)]

Protocol Amendment 3, Date 29 JUL 2010, [GlaxoSmithKline Document Number [RM 2007/00471/04](#)]

Protocol Amendment 4, Date 29 MAR 2012, [GlaxoSmithKline Document Number [RM 2007/00471/05](#)]

Protocol Amendment 5, Date 10 OCT 2012, [GlaxoSmithKline Document Number [RM 2007/00471/06](#)]

Protocol Amendment 6, Date 29 NOV 2012, [GlaxoSmithKline Document Number [RM 2007/00471/07](#)]

In this document the IDMC Charter refers to the Charter for the Independent Data Monitoring Committee, Version 1 (for Protocols: Phase III Program LPL100601 and SB480848/033), Report Date 13-FEB-2009 and Charter for the Independent Data Monitoring Committee, Version 2 (for Protocols: Phase III Program LPL100601 and SB-480848/033), Report Date 18-DEC-2009 and Charter for the Independent Data Monitoring Committee, Version 3 (for Protocols: Phase III Program LPL100601 and SB-480848/033), Report Date 19-JUN-2012.

After completion of both STABILITY and SOLID-TIMI 52, the data from both of these studies will be analyzed together in an integrated analysis to be described in a separate Integrated Reporting and Analysis Plan.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

Protocol Amendment 5 changed the primary endpoint of the study from major adverse cardiovascular events (MACE) to major coronary events prior to unblinding of treatment assignment. This RAP describes the planned analyses based on this amendment.

Primary Objective

The primary objective of this study is to evaluate clinical efficacy of long-term treatment with darapladib enteric coated (EC) tablets, 160 mg (oral once daily dose) as compared to placebo when added to standard of care in an ACS patient population on the incidence of first occurrence of the composite of major coronary events, i.e., coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), and urgent coronary revascularization for myocardial ischemia.

Secondary Objectives

The secondary objectives are to evaluate the efficacy of darapladib on major adverse cardiovascular events (MACE: cardiovascular (CV) death, non-fatal MI, and non-fatal stroke); the individual components of MACE; the individual components of major coronary events; total coronary events (defined as CHD death, non-fatal MI, urgent and non-urgent coronary revascularization, or hospitalization for unstable angina (UA)); any coronary revascularization procedures; the composite of all-cause mortality, non-fatal MI

and non-fatal stroke; the composite of CHD death and non-fatal MI; and all-cause mortality. Additional safety and efficacy parameters including relations to and changes of biomarkers of CV risk, health economic outcomes, and adverse events (AEs) will also be evaluated.

2.2. Study Endpoint(s)

The original primary endpoint of the study was MACE and was amended to major coronary events (defined as the composite of CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia) prior to unblinding the study data and without communication from the IDMC.

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all clinical events that constitute the composite endpoint of MACE (i.e., CV death, non-fatal MI, and non-fatal stroke) and other efficacy endpoints (i.e., urgent coronary revascularization for myocardial ischemia, hospitalization for unstable angina, heart failure requiring hospitalization). In addition, the CEC will confirm the cause of death as cardiovascular or non-cardiovascular. Cardiovascular death will be further defined as related to CHD when appropriate. The CEC's decision will be used as the adjudicated result. Therefore all components of major coronary events were also adjudicated by the CEC.

The classification of endpoints in this section as “primary”, “secondary” or “other”, reflects the organization presented in the protocol. Section 4.1.1.1, Section 8.3, Section 11.2, and Section 18.3 make reference to endpoints for which Type I Error is controlled by means of multiplicity adjustments. Specifically these endpoints include:

- Time to the first occurrence of major coronary events (the primary endpoint)

Other endpoints of interest for which Type I Error will be controlled:

- Time to first occurrence of the composite of CHD death and non-fatal MI
- Time to first total coronary event
- Time to first MI (fatal and non-fatal)
- Time to first coronary revascularization (See qualification below.)
- Time to CHD death
- Time to All-cause mortality

Per Protocol Amendment 1, coronary revascularizations planned prior to randomization but occurring after randomization will be excluded from the coronary revascularization endpoint definition. This exclusion also extends to composite endpoints for which coronary revascularization is a component. However, urgent coronary revascularization for myocardial ischemia or revascularization as a treatment for a myocardial infarction will be counted even if the investigator noted that it was pre-planned. Coronary revascularizations considered ‘not-urgent’ which were noted as pre-planned by the investigator will be excluded.

Section 9.3.7.5 and Section 9.3.7.6 describe subject level assessment windows used to identify events used in statistical analyses.

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to the first occurrence of any component of the composite of major coronary events, which consists of the following:

- CHD death
- Non-fatal MI
- Urgent coronary revascularization for myocardial ischemia.

See Protocol Section 6.3.1.1, Section 6.3.1.2, and Section 6.3.1.3 for descriptions of CHD death, non-fatal MI, and urgent coronary revascularization for myocardial ischemia associated with this study.

2.2.2. Secondary Efficacy Endpoints

The trial has the following key secondary endpoints:

- Composite measure of MACE which consists of time to the first occurrence of
 - CV death
 - Non-fatal MI
 - Non-fatal stroke
- Composite measure of **Total Coronary Events** which consists of time to the first occurrence of
 - CHD death
 - Non-fatal MI
 - Hospitalization for UA
 - Any coronary revascularization procedures (excluding coronary revascularization planned prior to randomization)
- Time to **CHD death**
- Time to **CV Death**
- Time to first occurrence of **MI** (fatal and non-fatal)
- Time to first occurrence of **Stroke** (fatal and non-fatal)
- Time to first occurrence of **Urgent Coronary Revascularization** for myocardial ischemia
- Time to first occurrence of **Any Coronary Revascularization** procedure (excluding coronary revascularization planned prior to randomization)
- Time to first occurrence of the composite of **All-Cause Mortality, Non-Fatal MI or Non-Fatal Stroke**

- Time to the first occurrence of the composite of **CHD death and non-fatal MI**
- Time to **All-Cause Mortality**

2.2.3. Other Endpoints

The trial has the following additional efficacy endpoints:

- Total incidence of first and subsequent coronary events comprising major coronary event or more specifically, time to all major coronary events (first and subsequent)
- Total incidence of first and subsequent CV events comprising MACE or more specifically, time to all MACE (first and subsequent)
- Time to first occurrence of **Heart Failure Requiring Hospitalization**
- Time to first occurrence of **Total Vascular Events** which consists of:
 - MACE
 - Hospitalization for UA or for any other non-coronary ischemic event (including TIA events as indicated by the adjudication committee)
 - Any revascularization procedure (coronary or non-coronary but excluding coronary revascularizations planned prior to randomization)
 - Limb amputation due to vascular causes
- Time to first occurrence of the composite of **Total Coronary Events, Excluding Target Lesion Revascularization in subjects treated with PCI prior to randomization**, which consists of:
 - CHD death
 - Non-fatal MI
 - Hospitalization for unstable angina
 - Any coronary revascularization procedure, excluding target lesion revascularization and procedure planned prior to randomization
- Time to **New Onset Diabetes Mellitus**.
- **Chronic Inhibition of Plasma Lp-PLA₂ Activity**
- **Health Care Resources Utilization**

2.2.4. Endpoints Related to Substudies or Investigations

- CV risk biomarkers and genetic assessments (see Section 15 and Section 16)
- Pharmacokinetic parameters (See Section 18.4)
- Sleep questionnaire (See Section 10.3.3, Appendix 718.7)

2.2.5. Other Assessments

Blood samples for clinical laboratory tests will be collected at baseline and at several time points post-randomization. Vital signs, electrocardiograms (ECGs), clinical laboratory safety tests and adverse event assessments will be performed to evaluate the safety and tolerability of darapladib.

2.3. Statistical Hypotheses

The primary endpoint of this study is the time to first occurrence of any component of the composite of major coronary events. See Section 2.2.1 for more details.

Subjects will be randomized into one of the following treatment groups:

- Placebo
- Darapladib (SB480848) EC tablets, 160mg

Let λ_d , λ_p be the respective hazard rates for the primary composite of major coronary events in the darapladib group and placebo groups, respectively. The hazard ratio, $HR = \lambda_d/\lambda_p$. The null and alternative hypotheses to be tested are the following:

- Null hypothesis: The hazard ratio for major coronary events for darapladib relative to placebo is equal to one (i.e., $H_0: HR = 1$). This is equivalent to no change in risk.
- Alternative hypothesis: The hazard ratio for major coronary events for darapladib relative to placebo is not equal to one (i.e., $H_1: HR \neq 1$, a two-sided test). This is equivalent to a change in risk not equal to zero.

The study is designed to show superiority of treatment with darapladib relative to placebo (i.e., hazard ratio less than one, or equivalently a reduction in risk greater than zero) when added to background of standard care.

The strength of evidence for rejecting the null hypothesis will be assessed using a two-sided p-value for testing the hypothesis that the observed hazard ratio is significantly different from one. At least two interim analyses are planned to assess efficacy. Futility may also be considered after an appropriate amount of data has been collected (see Section 4.1). A flexible alpha-spending function will be applied to account for the actual number and timing of interim assessments made by the Independent Data Monitoring Committee (IDMC). The final alpha for the trial will be adjusted accordingly. The details of this alpha-spending function are described in Section 4.1 and stopping guidelines can be found in the IDMC Charter. The primary endpoint of the trial was MACE at the time of the interim analyses.

2.4. Pharmacokinetic (PK) and PK/Pharmacodynamic (PD) objectives

Primary

Establish a population PK model adequate to describe the time-course and variability of plasma darapladib concentrations following repeat dose administration of Darapladib Enteric Coat Tablets, 160 mg in patients with ACS.

Secondary

Establish a population PK/PD model adequate to describe the relationship between plasma darapladib concentration and plasma Lp-PLA₂ activity following repeat dosing of Darapladib Enteric Coat Tablets, 160 mg in patients with ACS.

See Section 18.4 for further details related to the population PK substudies. Additionally, analysis plans for the PK substudy data are described in a separate Data Analysis Plan (DAP).

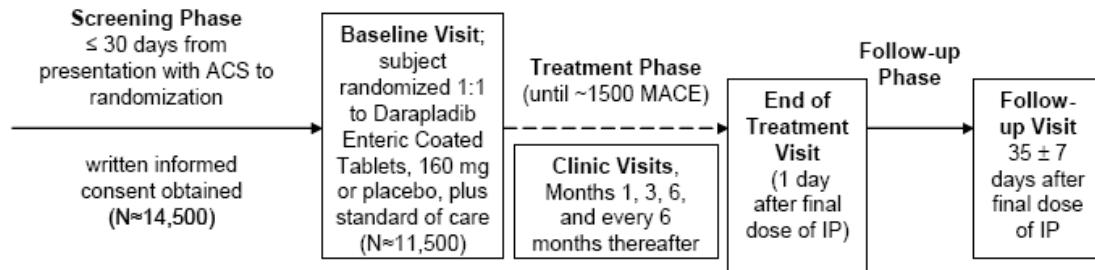
3. STUDY DESIGN

Section 5 makes reference to decision to increase sample size from 11500 to 13000. Further, protocol amendment 5 (made prior to unblinding data for SOLID-TIMI 52 (Study SB-480848/033) and without communication from the IDMC) changed the primary efficacy endpoint from MACE to major coronary events. The remainder of this section reflects assumptions made during the original protocol design. MACE was the endpoint on which the sample size estimates were based.

This study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event driven trial. The duration of the study will be determined by the rate of first occurrence of clinical events that comprise the composite endpoint of MACE. Subjects will be encouraged to remain in the study after their MACE and continue on-treatment for the duration of the trial until the target number of events is achieved. The study will be terminated when it is projected that approximately 1500 reports of first occurrence of MACE have occurred. Based on current assumptions, the median treatment duration is anticipated to be approximately 3 years.

Approximately 14,500 subjects with ACS are planned to be screened in order to randomize a minimum of approximately 11,500 total subjects, or at least 5750 subjects per treatment arm. It is planned that subject accrual will occur across a minimum of approximately 900 sites worldwide over a minimum period of approximately 24 months.

A schematic diagram of the main study design is presented in [Figure 1](#).

Figure 1 SOLID-TIMI 52 Study Design Schematic

4. PLANNED ANALYSES

4.1. Interim and Final Analyses

In discussions of interim and final analyses, MACE accrual refers to the events adjudicated by the CEC as MACE (see Section 2.2 for more details).

4.1.1. Evaluation of Efficacy

The appropriate alpha levels for testing primary, secondary, and other endpoints are described below and are presented in Section 18.3.

The IDMC will review data periodically throughout the trial. Formal interim analyses will be performed for assessment of efficacy after approximately 850 and 1150 first occurrence MACE have accrued. The IDMC will consider stopping the trial early for efficacy only for a very large efficacy benefit for MACE or all-cause mortality, with consideration given to the consistency of effect between the two parameters. The IDMC Charter provides guidance for stopping for substantial benefit. The IDMC will also monitor all-cause mortality. The IDMC Charter provides guidance for stopping for substantial benefit.

The IDMC will use a flexible alpha-spending function to create a stopping boundary for MACE. The IDMC may consider terminating the trial early if this threshold is achieved, but it will also consider other aspects of the study including the size of the safety database and the consistency of effects across subgroups of interest. The IDMC Charter describes these criteria and provides suggestions for the IDMC on stopping the trial for efficacy.

4.1.1.1. MACE Evaluation Strategy

Alpha spending will be based on a target final event count of 1500 first occurrence MACE. The spending function will be the power function, where the cumulative alpha $\alpha(t) = \alpha t^\phi$ with parameter ϕ selected to achieve a nominal two-sided type I error of $\alpha=0.001$ at $t=1150/1500$ (i.e., $\phi=13.8$). For early interim assessments, the critical values will be truncated at $\alpha=0.0005$ resulting in a nominal two-sided $p<0.0005$ for an assessment after approximately 850 events and $p<0.001$ after approximately 1150 events have accrued. If the interims occur as planned at 850 and 1150 events, then the final analysis of the primary endpoint will use $p=0.0499$ for testing. See Section 18.3 for a graphical depiction of the efficacy endpoint testing strategy.

If the trial is stopped at an interim because of compelling efficacy, then the alpha levels set by this alpha spending function will be used as the threshold for assessing the efficacy on MACE. For the final analysis, the unspent alpha based on this alpha spending function will be used as the threshold for assessing the primary endpoint.

4.1.1.2. Secondary and Other Endpoint Evaluation Strategy

A group of endpoints has been defined which consists of first occurrence of MI (fatal and non-fatal), first occurrence of any coronary revascularization, CV death, and all-cause mortality. This group will be tested in a hierarchical manner using the significance level specified for testing the primary endpoint if the trial is stopped early after an interim assessment. (see Section 8.3). This hierarchy was revised based on Protocol Amendment 5 to include the first occurrence of the composite of CHD death and non-fatal MI as well as the first occurrence of total coronary events, and will be tested using the final alpha level as defined by the alpha spending function, provided the primary endpoint is significant at the same alpha level. A point estimate, 95% CI, and descriptive p-value will be generated for all of the remaining endpoints that are not included in this group (see Section 2.2). Evaluation of Safety

The IDMC chair will monitor serious adverse events (SAEs) and withdrawals quarterly. The IDMC will monitor additional safety measures as appropriate. The IDMC Committee will meet at least every 6 months (or more frequently if requested by the IDMC) to review the safety data and will assess harm on the basis of the evidence of the data and clinical judgment of the members of the IDMC. Specifically, the IDMC will review SAEs, lab abnormalities, and vital signs of clinical concern for identification of any potential safety signals.

No adjustment to the final alpha level for efficacy has been made based on any safety stopping guideline. At each periodic review, a flag based on $p<0.01$ for harm will be used to assess MACE, all-cause mortality, and CV mortality. This flag will signal further examination of all available data by the IDMC, with consideration of altering the study conduct or terminating the study. If this flag is triggered at any review, the totality of all available data will be used in any recommendation for stopping or altering the trial.

4.1.2. Evaluation of Futility

The IDMC may consider stopping the trial for futility. This assessment is best conducted after a sufficient number of events have occurred and the study has had a reasonable duration. Hence, the IDMC will not consider futility until at least 2 years of study duration and at least two-thirds of MACE have occurred (approximately 1000 events). Therefore, futility is likely to be assessed at the second planned interim analysis for efficacy.

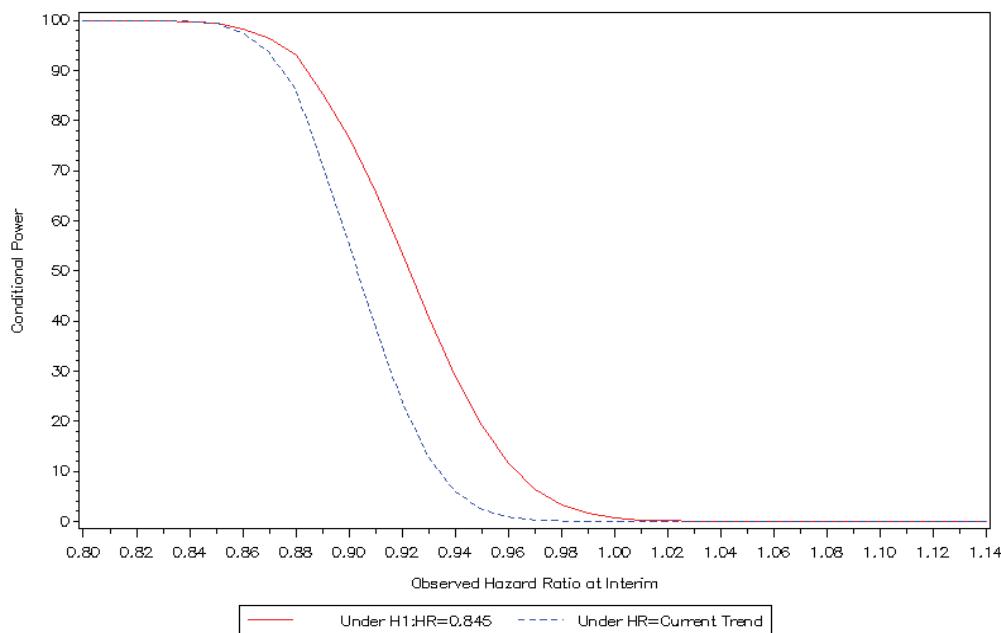
Futility will be assessed using conditional power where power for the study is recalculated on the basis of the results observed up to the time of the interim analysis. If this conditional power to detect a favorable outcome for the MACE endpoint is very low and the IDMC predicts that the trial is unlikely to demonstrate a statistically significant benefit when completed, then the IDMC may consider stopping the trial for futility, with consideration for all other aspects of the trial. See IDMC Charter for further details.

[Table 1](#) presents the expected conditional power for a range of scenarios at the second planned interim analysis. Additionally, [Figure 2](#) presents a wide range of conditional power estimates at the planned interim assessment.

Table 1 Estimated Conditional Power at the Planned Interim Analyses

Conditional power for significance at end of study		Hazard Ratio observed at Interim 2 (1150 Events)			
		0.845	0.90	0.95	1.0
Underlying Hazard Ratio	0.845	99%	77%	18%	0.7%
	0.90	98%	57%	7%	0.1%
	0.95	94%	37%	2%	<0.1%
	1.0	87%	21%	0.7%	<0.1%

Figure 2 Observed Hazard Ratio versus Conditional Power Under the Alternative Hypothesis $H_1:HR=0.845$ and Under Current Trend, After 1150 Events



4.1.3. Other Considerations at the Interim Analyses

An independent Statistical Data Analysis Center (SDAC) will perform the unblinded interim analyses and periodic safety updates and deliver them to the IDMC.

The IDMC will receive analyses of primary and key secondary endpoints by geographic region.

If the study stops because of results of the interim analysis, subjects will be brought to the investigational sites for the final study visits (end of treatment visit and follow-up visit) whenever possible.

If the trial is stopped for any reason other than for efficacy (e.g., for safety or futility), point estimates, 95% confidence intervals, and p-values will be generated for the primary and key secondary endpoints. P-values will be compared against a nominal two-sided 0.05 level and will be provided for descriptive purposes only.

If the trial is stopped early because of efficacy, all analyses described in this RAP will be generated. If the trial is stopped because of safety or futility, only the most relevant analyses will be performed.

4.1.4. Final Analysis

Final analyses, which will include all planned analyses, will be performed after the database is final. The study statistician will then unblind the study in RandAll, a system used by GSK to store the unblinded treatment codes. The treatment codes will then be merged with the rest of the clinical data for analysis. An independent copy of the trial database will also be sent to the TIMI Study Group at Brigham and Women's Hospital in Boston, MA.

GSK clinical personnel and the TIMI Study Group will review blinded data on an ongoing basis throughout the trial to review coding of concomitant medications and adverse events, as well as any other data points as needed. If in any of these situations a decision must be made with respect to classifying the data, the clinical decision from the blinded data review will be considered final.

5. SAMPLE SIZE CONSIDERATIONS

In April 2011, the sponsor in conjunction with TIMI and the SOLID-TIMI 52 Executive Steering Committee agreed to increase the sample size to 13000 in order to maintain the planned median follow-up time after accounting for the observed enrollment and event rates.

The remainder of this section reflects assumptions made during the protocol design.

5.1. Sample Size Assumptions

This event driven study is designed to have 90% power to detect a 15.5% reduction in risk of MACE (hazard ratio=0.845) for subjects treated with darapladib compared to placebo on top of a background of standard care. Assuming a placebo event rate of approximately 7.5% for the first year and 3.5% per year thereafter, with an overall type I error rate (alpha level) of 5%, a total of 1500 MACE events are required to achieve approximately 90% power. Components of the MACE composite endpoint are expected to make up approximately 20% events from CV death, 60% events from non-fatal MI, and 20% events from non-fatal stroke. All subjects will be followed until the required total number of events occurs.

The sample size calculation accounts for two sources of subject withdrawal that are assumed to be uniformly distributed over the duration of the study. There is expected to be an annual rate of 1% of subjects not assessable due to loss to follow-up, who will be censored at the time of withdrawal. In addition, subjects may stop taking study medication, but will continue to be followed up for outcomes. The hazard ratio of 0.845 accounts for an 8% annual discontinuation from treatment and is based on a weighted average of an on-therapy hazard ratio of 0.83 and a post-therapy hazard ratio of 1.0.

The IDMC will review data periodically throughout the trial as described in Section 4.1. A small p-value will be applied to assess efficacy at each interim look, thereby preserving at least a type I error rate >0.048 (4.8% significance) for the final analysis. If the interims occur as planned at 850 and 1150 events, then the final analysis of the primary endpoint will use p=0.0499 for testing; the interim analyses under this spending function have a negligible effect on overall sample size required for the trial.

Assuming a recruitment duration of 24 months and the event rates above, a sample of size 11,500 would result in a total study duration of approximately 4.1 years (encompassing a projected median follow-up duration of approximately 3 years assuming uniform enrollment). If the enrollment pattern is J-shaped as opposed to uniform, the study duration will be extended by approximately 3-6 months. Sample size was calculated using EAST 5.1.

Center-based randomization is planned, where central randomization using permuted blocks is stratified according to center.

5.2. Sample Size Sensitivity

This is an event driven study, with the number of required events (1500) driven by the assumed treatment effect. If the true underlying reduction in risk is lower or higher than the assumed 15.5%, the power resulting from an observed 1500 MACE is shown in [Table 2](#).

Table 2 Assumptions for Power Calculation

Reduction in Risk	Hazard Ratio	Power
11%	0.89	61%
12.5%	0.875	73%
14%	0.86	83%
15.5	0.845	90%
17%	0.83	95%
18.5%	0.815	98%
20%	0.80	99%

If the placebo event rate is lower or higher than the assumed first year rate of 7.5% and subsequent annual rate of 3.5%, the resulting study durations are shown in [Table 3](#) (assuming the sample size remained fixed).

Table 3 Sample Size Sensitivity for 90% Power and 15.5% Reduction in Risk

Placebo First Year Event Rate	Placebo Post First Year Event Rate	Study Duration (n=11,500)
8%	4%	3.7
7.5%	4%	3.8
7%	4%	3.9
8%	3.5%	3.9
7.5%	3.5%	4.1
7%	3.5%	4.2
8%	3%	4.2
7.5%	3%	4.4
7%	3%	4.6

5.3. Sample Size Re-estimation

The event rate will be monitored using data blinded with respect to treatment assignment. Should the observed event rate be lower than anticipated or discontinuation rates (i.e., withdrawal from study or discontinuation of IP) higher than expected, then the sponsor and the Steering Committee will review the value of sample size re-calculation and a potential increase in study size or in number of events based on blinded data reviews.

The maximum sample size will be capped at 15,000 randomized patients. Sample size re-calculation is most pragmatically implemented prior to completion of recruitment. Therefore, if recruitment has been closed out, the duration of the trial may be extended in order to achieve the target number of 1500 MACE.

6. ANALYSIS POPULATIONS

The following populations will be assessed:

Safety Population. This population consists of all randomized subjects who received at least one dose of investigational product. Subjects will be analyzed according to the treatment to which they were randomized. This population will be used for assessing safety.

All-Randomized (ITT) Population. This population, which will consist of all randomized subjects, will be the primary population for assessing efficacy. Subjects will be analyzed according to the treatment to which they were randomized. For reporting purposes, this population will be titled All-Randomized (ITT) for consistency with other previously reported studies.

7. TREATMENT COMPARISONS

7.1. Data Display Treatment and Other Sub-group Descriptors

In the study report data displays, the treatment group descriptors are the following, which are consistent with conventions used in previous studies of darapladib:

- Placebo
- SB480848 160mg

7.2. Primary Comparison of Interest

The primary comparison of interest is the hazard ratio of adjudicated major coronary events for subjects randomized to darapladib versus placebo. The All Randomized (ITT) population will be utilized for this comparison. Section 9.3.7.5 describes subject level assessment windows used to identify events used in statistical analyses.

The comparison will be made at an overall 5% significance level, adjusting for interim analyses using a flexible alpha-spending approach as described in Section 4.1.

7.3. Other Comparisons of Interest

Statistical significance will be declared for the group of endpoints, consisting of first occurrence of the composite of CHD death and non-fatal MI, first occurrence of total coronary events, first occurrence MI (fatal and non-fatal), first occurrence of any coronary revascularization, CHD death, and all-cause mortality, if the corresponding two-sided p-value for the hypothesis test comparing darapladib versus placebo is less than or equal to the significance level specified for the final analyses and any appropriate multiplicity adjustments described in Section 4.1 and Section 8.3. These endpoints will be evaluated using a hierarchical approach to testing as graphically depicted in Section 18.3. Treatment comparisons will be performed for all of the remaining endpoints described in Section 2.2 for descriptive purposes.

7.4. Integrated Analyses

This trial, which is designed to assess ACS patients, is planned to be conducted in conjunction with a second mutually supportive outcomes trial of similar design in chronic heart disease patients. Upon completion of both trials, the data from both of these phase III outcome trials may be combined to provide an assessment of the overall clinical efficacy and safety of darapladib. Further details, including methods to address multiplicity and strategies for combining the data from these two trials, are described in a separate Summary Data Analysis Plan.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The SAS System, Version 9 (or higher) for UNIX will be used for all analyses, unless otherwise specified. Additionally, R Version 2.15 or higher may be used for the production of graphics.

No imputation will be made for any missing numerical data unless specified.

If screen failure data is captured in the electronic case report form (eCRF) system or through vendor data, it will not be included in datasets provided to the statistics and programming group for inclusion in any summaries.

8.1. Multicenter Studies

In this multicenter international study, enrolment will be presented by investigative site, country, and the regions defined in Table 4. Sub-regions of importance will be defined with consideration for standard of care medical practice, number of subjects enrolled, and regulatory considerations. These include (but are not limited to) those identified in Table 4.

Table 4 Region Definitions

Region	Countries
North America	USA, Canada
Eastern Europe	Bulgaria, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, Turkey, Ukraine
Western Europe	Belgium, Denmark, France, Germany, Israel, Italy, Netherlands, South Africa, Spain, Sweden, United Kingdom
South America	Argentina, Brazil, Chile, Columbia, Perú
Asia/Pacific	Australia, China, India, Japan, Korea, New Zealand, Philippines, Taiwan, Thailand
Sub-region: East-Asia	China, Japan, Korea, Taiwan

Randomization is stratified by center to ensure balance across treatment groups and will not be taken into account within the analysis models.

For any summaries which include information related to a subject's center or investigator, the most recent center and investigator at the time that the database is final will be used.

8.2. Examination of Covariates or Subgroups

The following is a list of subgroups and covariates of specific clinical interest that will be used in analyses. Additional subgroups or covariates of clinical interest may be considered in the future. If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial or if the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup instead.

- Diagnosis of ACS per Protocol Inclusion Criteria 3: (UA/NSTEMI/STEMI)
- Diagnosis of ACS will also be categorized as STEMI and NSTEMI+UA
- Elevated troponin or CK-MB during qualifying event (yes/no)
- ST-segment deviation during qualifying event (yes/no)
 - ST-segment deviation is defined as transient ST elevation **or** persistent ST elevation **or** dynamic ST depression at the screening ECG
- PCI performed for qualifying event (yes/no)
- Catheterization (coronary angiography) performed for qualifying event (yes/no)
- Additional predictors of CV risk
 - Age \geq 60 years at randomization (yes/no)
 - Prior history of documented MI (yes/no)
 - Diabetes mellitus requiring pharmacotherapy (yes/no)
 - Significant renal dysfunction (defined as estimated glomerular filtration rate [eGFR] \geq 30 and \leq 59 mL/min per 1.73 m²) (yes/no)

- Polyvascular disease manifested as coexistent clinically diagnosed arterial disease in at least 2 arterial territories (See Protocol.) (yes/no) If yes, then breakdown:
 - Cerebrovascular disease defined as carotid artery disease or as prior ischemic stroke that occurred > 3 months prior to randomization
 - Peripheral artery disease
 - Peripheral stenting or surgery (including amputation)
 - Intermittent claudication
 - Ankle brachial index decreased (<0.9 in at least one ankle)
- Number of known additional predictors of CV Risk (1, 2, ≥3) (derived from the five additional predictors of CV risk above, not considering the sub-bullets; with missing counted as 0)
- Other CV risk factors
 - Baseline high-density lipoprotein cholesterol [HDL-C] level <40 mg/dL (1.03 mmol/L) (yes/no)
 - Smoked within 3 years of randomization [yes/no]
 - Prior PCI (yes/no)
 - Prior CABG (yes/no)
 - Prior coronary revascularization (PCI/CABG) (yes/no)
 - Any cardiovascular conditions of interest: abdominal aortic aneurysm , angina pectoris, atrial arrhythmias, congestive heart failure, hyperlipidemia, hypertension, moderate to severe valvular disease) (yes/no)

Demographics/Other Baseline Endpoints

- Ethnic group (Hispanic/Latino, Not Hispanic/Latino)
- Race group (White, Black, Central/South/South East Asian, East Asian/Japanese, Other)
- FDA race group (American Indian or Native Alaskan, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race)
- Race group collapsed (White, Non-white)
- Geographic region (North America, Eastern Europe, Western Europe, South America, Asia/Pacific)
- Sub-region (East Asia)
- Country
- United States (US, Non-US)
- Gender (Male, Female)

- Age at randomization (<65, 65-74, ≥ 75)
- Baseline diabetes status (with or without pharmacotherapy) (yes/no)
- Baseline blood pressure (Target, High)
 - **Target:** Both systolic and diastolic BP are <130/80 mmHg for diabetic subjects or subjects with chronic kidney disease; both systolic and diastolic BP are < 140/90 mmHg for all other subjects (both SBP and DBP must meet target levels)
 - **High:** Either systolic or diastolic BP is $\geq 130/80$ mmHg for diabetic subjects or subjects with chronic kidney disease; either systolic or diastolic BP is $\geq 140/90$ mmHg for all other subjects
- Baseline estimated glomerular filtration rate [eGFR] (<60 ml/min/1.73m², ≥ 60 ml/min/1.73m² or equivalently <1 ml/sec/1.73m², ≥ 1 ml/sec/1.73m²)
- Baseline low-density lipoprotein cholesterol [LDL-C] (<1.80 mmol/L, ≥ 1.80 - <2.58 mmol/L, ≥ 2.58 mmol/L)
- Baseline HDL-C (<1.03 mmol/L, ≥ 1.03 -<1.55 mmol/L, ≥ 1.55 mmol/L)
- Baseline Lp-PLA₂ activity levels (tertiles of the entire study cohort where the tertiles are defined as $\leq=33.33\%$, $>33.33\%$ to $\leq=66.66\%$, and $>66.66\%$). See Section 14.2 for more details.
- Family history of premature CHD (Male family member $\leq=55$ years or female family member $\leq=65$ years) (yes/no)
- Body mass index at baseline (<25, 25-<30, ≥ 30 kg/m²)
- Waist/hip ratio at baseline (Level 1, Level 2, Level 3) [Yusuf, 2004]
 - Level 1: ≤ 0.90 for males, ≤ 0.83 for females
 - Level 2: >0.90 – ≤ 0.95 for males, >0.83 – ≤ 0.90 for females
 - Level 3: >0.95 for males, >0.90 for females
- Baseline aspirin use (yes/no)
- Baseline statin use (yes/no)
- Statin use for at least 8 weeks prior to randomization (yes/no)
- Baseline beta-blocker use (yes/no)
- Baseline P2Y12 inhibitor use (yes/no)
- Baseline ACE Inhibitor or Angiotensin II Receptor Blocker (yes/no)
- Smoking status (Current smoker, former smoker, never smoked)

For the purposes of assessing balance between treatment arms, t-tests (or signed-rank tests if distributions are skewed) will be conducted on all continuous variables used to form the subgroups described in this section. Similarly, for binary and categorical variables used to form subgroups, tests of proportions and chi-square goodness of fit tests

will be used. The p-values from these tests are produced for descriptive/exploratory purposes.

The following subgroups will be excluded from statistical summaries and models due to low percentages of subjects in certain categories: sub-region and country.

The following subgroups will be excluded from statistical models except for those models including only the subgroup or its interaction with treatment due to either low percentages of subjects in certain categories or similarities with other subgroups: diagnosis of ACS (STEMI, NSTEMI, UA), additional predictors of CV risk: diabetes requiring pharmacotherapy, additional predictors of CV risk: significant renal dysfunction, other CV risk factors: HDL-C <40mg/dL, other CV risk factors: smoking use, other CV risk factors: prior PCI, other CV risk factors: prior CABG, other CV risk factors: prior PCI or CABG, other CV risk factors: any prior CV condition of interest, ethnicity, race group, FDA race group, age at randomization, waist/hip ratio at baseline, baseline aspirin use, baseline statin use, statin use at least 8 weeks before randomization, baseline beta-blocker use, baseline P2Y12 inhibitor use, baseline ACE inhibitor or Angiotensin II receptor blocker use.

8.3. Multiple Comparisons and Multiplicity

Issues related to multiplicity arising from performing tests at several interim analyses and at the final analysis are addressed in Section 4.1.

Issues related to multiplicity arising from testing the primary endpoint, secondary endpoints, and other endpoints will be addressed as described below.

The primary endpoint of major coronary events will be tested first using the alpha level specified by the alpha-spending function (Section 4.1).

If major coronary events shows a statistically significant benefit, then the endpoints will be tested using a hierarchical strategy based on closed testing procedures to account for multiplicity, at the same alpha level as the primary endpoint is tested. This group of endpoints will be tested in the following order:

1. Time to first occurrence of the composite of CHD death and non-fatal MI
2. Time to first occurrence of total coronary events
3. Time to first occurrence of MI (fatal and non-fatal)
4. Time to first occurrence of any coronary revascularization procedure
5. Time to CHD death
6. Time to all-cause mortality

No adjustment for multiplicity will be made for the remaining secondary and other endpoints. These endpoints will be used in a supportive nature to evaluate consistency and further confirmation of efficacy of the treatment groups with respect to major coronary events.

9. DATA HANDLING CONVENTIONS

9.1. Selection of Baseline Values

For purposes of data analyses, the baseline value of a particular type of assessment for a given subject will be defined as the latest assessment on or prior to the date of randomization.

9.2. Premature Withdrawal and Missing Data

9.2.1. Discontinuation of IP and Emergency Unblinding

Subjects who permanently discontinue IP before the study end are expected to remain in the study until its planned completion. These subjects will be encouraged to continue taking IP until the day before the End-of-Treatment/Early Withdrawal visit. If they do not wish to continue taking IP until the day before this visit, then the End-of-Treatment/Early Withdrawal visit will not be done and the subject will be scheduled for a Follow-up Visit. Study endpoints, especially MACE, should be reported between the Follow-up visit and the end of the study. In addition SAEs which are assessed as related to IP, related to study participation (e.g., protocol-mandated procedures, invasive tests, or study related changes in existing therapy), or related to a GSK concomitant medication should also be reported. In subjects withdrawing consent to provide any additional information, no further study visits or study-related telephone contacts can be conducted. Additional information regarding vital statistics will be collected if it is available to the public.

Subjects can be followed after discontinuing from IP through telephone follow-up or through third-party follow-up. During the follow-up period, study endpoints will be assessed. The date that the third-party contact was last able to assess endpoints will be collected for use in defining analysis periods as described in Section 9.3.7.

The investigator or treating physician may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. If a subject is unblinded in this situation, the subject's data will be included in analyses regardless of unblind status.

9.2.2. Study Completion and Study Withdrawal

A subject is considered to have withdrawn from the study if the answer to the question "Was the subject withdrawn from the study before study reached GSK target number of primary clinical endpoints?" on the Study Conclusion eCRF page is answered 'Yes'; otherwise the subject is considered to have completed the study. The date of completion or withdrawal as entered on this eCRF page will be used as the study completion date for both subjects who completed the study and subjects who withdrew from the study.

Note: Subjects withdrawing from the study include subjects who actively withdraw (and formally withdraw their consent) or are lost to follow-up (who are presumed to have not withdrawn their consent).

Every effort will be made to gather all available information on subjects prior to GSK stopping the study when the target number of MACE has been achieved. There will be a date at which the database will close and the sites will be unable to enter any further data. At this time point, any subjects who were unable to be contacted will have their data entry end at this time point. If GSK is alerted to any data after this time point and prior to unblinding, this data may be described in the clinical study report but will not be included in the database used for analysis purposes.

9.2.3. Missing Data

When available, reasons for missing data will be examined to evaluate the potential for bias in the analysis.

No imputation will be made for any missing numerical data, unless otherwise specified. Missing data will generally not be considered in the calculation of percentages (i.e., the denominator will not include subjects who have missing data at a given time point).

9.3. Derived and Transformed Data

The following describes the use of derived or transformed data.

9.3.1. General

- Randomization date = Date subject was randomized
- Safety population = A subject is considered to be in safety population if the subject was randomized and either there is evidence that the subject had taken at least one dose of drug or there is insufficient evidence to prove that the subject had not taken any drug. Consequently, a randomized subject to be included in the safety population must have either a non-missing treatment start date or a bottle dispensed from which the drug consumption is either missing or greater than zero.
- First IP start date = IP start date for the first visit at which IP was dispensed
- Last IP stop date = IP end date for the last visit at which IP was dispensed
- Treatment start date = First dose of IP start date, or if missing, the randomization date only for subjects who are in the safety population
- Treatment stop date = Last IP stop date or, if missing, the study completion/withdrawal only for subjects who are in the safety population
- Study completion/withdrawal date = Date of withdrawal for subjects withdrawing (i.e., subjects who actively withdraw or deemed lost to follow-up) from study or date of completion of study for subjects who complete the study (per Section 9.2.2)

Note: Subjects who die while on study are considered as having completed the study.

- Study day = the number of days from randomization date
 - If the reference date is missing, the study day will be missing

- If the reference date is less than the randomization date, then study day = reference date – randomization date
- If the reference date is equal to or more than the randomization date, then study day = reference date – randomization date + 1
- Treatment day = the number of days from treatment start date
 - If the treatment start date is missing, the treatment day will be missing
 - If the reference date is less than the treatment start date, then treatment day = reference date – treatment start date
 - If the reference date is equal to or more than the treatment start date, then treatment day = reference date – treatment start date + 1
- Last day on study excluding follow-up visit =
 - the end of treatment visit date for subjects who completed the study on IP
 - the treatment stop date for subjects who completed the study on IP but does not have an end of treatment visit(for subjects who die while on IP, the date of death will be used)
 - the study completion date for subjects who withdrew from the study early (i.e., subjects who actively withdraw or deemed lost to follow-up) or who discontinue from IP
- Baseline value = the latest value evaluated on or before the randomization date
- Change from baseline = Post-baseline – Baseline
- Percent change from baseline = $100 \times (\text{Post-baseline} - \text{Baseline}) / \text{Baseline}$
- End of treatment value = the latest value evaluated on or before either the (treatment stop date + 1) or, if the treatment stop date is missing, the study completion date(for subjects who have a non-missing treatment start date)
- End of study value = the latest value evaluated on or before the study completion date
- First study contact date = first study contact with the subject while on the study
- Last study contact date = last study contact (clinic or telephone visit) with the subject while on the study
- For purposes of calculation, time will be defined in the following manner according to GSK standard principles:
 - 1 week = 7 days
 - 1 month = 30.4375 days
 - 1 year = 365.25 days

9.3.2. Missing Values and Partial Values

- Missing start dates: Impute the first possible date
 - If only the day of month is missing, impute the first day of the month (e.g. --MAR2007 would impute as 01MAR2007)
 - If the month and day of month are missing, impute 01JAN (e.g., ----2007 would impute as 01JAN2007)
 - If the year, month, and day of month are missing, do not impute the date
- Missing stop dates: Impute the last possible date
 - If only the day of month is missing, impute the last day of the month (e.g. --MAR2007 would impute as 31MAR2007)
 - If the month and day of month are missing, impute 31DEC (e.g., ----2007 would impute as 31DEC2007)
 - If the year, month, and day of month are missing, do not impute the date
- If the date last smoked for former smokers is missing the following will be imputed:
 - If only the day of the month is missing, impute the last day of the month unless this date is after the screening date, in which case the screening date will be used.
 - If the month and day are missing, impute as 31DEC unless this date is after the screening date, in which case the screening date will be used.
 - If the year, month and day of the month are missing then the screening date will be used.
- If the date last known alive from a third party follow-up is a partial date then the rules above for missing stop date will be used.

Missing Event dates are discussed in Section [9.3.7](#).

9.3.3. Demographic Characteristics

- Age (years) at randomization = year of randomization date minus year of birth; if the month and day of randomization date are less than the month and day of birth then subtract 1
- Body Mass Index (kg/m^2) = weight (kg) / [height (m)]²
- Waist/Hip Ratio = Waist circumference (cm) / Hip circumference (cm)
- Geographic ancestry data will be combined into categories as provided by FDA and summarized as FDA race groups as self-reported by the subject:
 - American Indian or Alaskan Native
 - Asian (Asian-East Asian Heritage, Asian-Japanese Heritage, Asian-Central/South Asian Heritage, Asian-South East Asian Heritage, Asian-Mixed Race)

- Black (African American/African Heritage)
- Native Hawaiian or Other Pacific Islander
- White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, White-Mixed Race)
- Mixed Race (Multiple races are selected, but excludes Asian-Mixed Race and White-Mixed Race)

Note: Asian – Mixed Race includes subjects who have more than one Asian category selected, but no other categories. White – Mixed Race includes subjects who have more than one White category selected, but no other categories.

- Geographic ancestry data will be combined into categories and summarized as race groups as self-reported by the subject:
 - Black (African American/African Heritage)
 - East Asian/Japanese (Asian-East Asian Heritage, Asian-Japanese Heritage)
 - Central/South/South East Asian (Asian-Central/South Asian Heritage, Asian-South East Asian Heritage)
 - White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage)
 - Other (American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Mixed Races)
- Geographic ancestry data will be collapsed into simple categories and summarized as race group collapsed:
 - White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, White – Mixed Race)
 - Non-white (Any subjects with categories selected other than those that meet the definition for white above)
- Diabetic subjects include subjects with type I and type II diabetes mellitus
- Diabetic subjects requiring pharmacotherapy include subjects with type I diabetes mellitus and subjects with type II diabetes mellitus requiring pharmacotherapy.
- Chronic kidney disease (CKD) status (defined as subjects who have eGFR ≥ 30 and ≤ 59 mL/min per 1.73m² OR subjects who have a urine ACR ≥ 30 mg albumin/g Creatinine)

9.3.4. IP Discontinuation, Study Withdrawal, Compliance and Exposure

- IP Discontinuation Censored Time (Days) = (Last day on study excluding follow up visit – Randomization date) + 1

Note: In the case where a subject on IP is lost to follow-up, a final IP stop date is presumed, though unobserved. In this case, the last point of contact of the patient is used for both the IP stop date and withdrawal date.

- Time to IP Discontinuation (Days) = (Treatment stop date – Randomization date) + 1
- IP Person Years = (Cumulative total of time to IP discontinuation for subjects who discontinued IP+ Cumulative total of IP censoring time for those who did not discontinue IP) / 365.25
- IP Discontinuation Incidence Rate (per 100 person years) = (100 * Number of subjects discontinued IP) / IP person years
- Study Censored Time (Days) = (Study Completion Date – Randomization date) + 1
- Time to Study Withdrawal (Days) = (Study withdrawal date – Randomization date) + 1
- Study Person Years = (Cumulative total of time to study withdrawal for subjects withdrawing from study+ Cumulative total of study censoring time for subjects who did not withdraw from study) / 365.25
- Study Withdrawal Incidence Rate (per 100 person years) = (100 * Number of subjects who have withdrawn from study) / Study person years
- Possible follow-up time (days) = Study completion date or date of the middle of the end of study window for subjects who did not complete the study – randomization date + 1
- Total possible follow-up time (person years) = Cumulative total of possible follow-up time (days) / 365.25
- Treatment Duration (days) = Treatment stop date – Treatment start date + 1
- Categories of Treatment duration will be created as follows: Missing, \leq 6 months, >6- \leq 12 months, >12- \leq 18 months, >18- \leq 24 months, etc...
- IP Exposure (days) = Treatment stop date – Treatment start date + 1; subtracting the number of days during treatment period when the subject temporarily stopped taking IP because of an Investigator-driven break
- Categories of IP exposure will be created as follows Missing, \leq 6 months, >6- \leq 12 months, >12- \leq 18 months, >18- \leq 24 months, etc...
- IP Exposure Person Years = Cumulative total of IP exposure (days) for all subjects / 365.25
- Study Duration (days) = Last day on study excluding follow-up visit – Randomization date + 1
- Treatment compliance is calculated as % compliance for the days subject was on-treatment during the entire study:

$$\begin{aligned} \text{\% treatment compliance} = \\ \frac{(\text{Total \# tablets dispensed} - \text{Total \# tablets returned})}{(\text{\# days of IP exposure})} \times 100 \end{aligned}$$

Note: Treatment compliance assesses the number of tablets taken while the subject was on IP and excludes days the subject stopped taking IP because of an Investigator-driven break.

- Scheduled visit compliance is calculated as % compliance for the days subject was on-treatment between the previous scheduled visit and the current scheduled visit:

$$\% \text{ visit compliance} =$$

$$\frac{(\# \text{ tablets dispensed at previous visit} - \# \text{ tablets returned at current visit})}{(\# \text{ days of IP exposure between visits})} \times 100$$

- Study duration compliance is calculated as % compliance for the days subject was on study, regardless of the date subject stopped taking IP:

$$\% \text{ study compliance} = \frac{(\text{Total } \# \text{ tablets dispensed} - \text{Total } \# \text{ tablets returned})}{(\# \text{ days of study duration})} \times 100$$

Note: If a bottle has been dispensed but never returned, the number of tablets consumed from that bottle cannot be determined; hence the information from that bottle will not enter the calculation of compliance.

Note: If more than 50% of a subject's dispensed bottles were not returned or have missing compliance information, then this subject's treatment compliance will not be calculated and will remain missing.

Note: For scheduled visit compliance calculations, if there is a missing end date at a particular visit then the end date will be imputed as the (start date of the next visit – 1 day).

- Categories of treatment compliance will be created as follows: missing, <80%, 80-120%, >120%
- Additional categories of treatment compliance will be created as follows: missing, <90%, 90-110%, >110% and missing, ≤100%, >100%

9.3.5. Adverse Events

- AE Onset Time Since First Dose (days):
 - if treatment start date ≤ AE onset date: AE onset date – treatment start date + 1
 - otherwise: missing
- AE Onset Time Since Last Dose (days):
 - if treatment stop date + 1 < AE onset date: AE onset date – treatment stop date + 1
 - otherwise: missing
- AE Duration (days): AE Resolution date – AE Onset date + 1
- Pre-Randomization AE: AE Onset date is before the randomization date

- Post-Randomization AE: AE Onset date is on or after the randomization date
- Pre-treatment AE: AE Onset date is before the treatment start date. Note: All AEs will be pre-treatment for subjects who did not take IP.
- On-treatment AE: AE Onset date is on or after the treatment start date and on or before (treatment stop date + 1). Note: Only defined for subjects who took IP.
- Post-Treatment AE: AE Onset date is after (treatment stop date + 1). Note: Only defined for subjects who took IP.

Note: AEs that occur during study medication interruption will be classified as Post-Randomization and On-treatment.

Note: If AE Onset date is missing and AE Resolution date is before the treatment start date, then the AE will be classified as Pre-Treatment. If AE Onset date is missing and AE Resolution date is either missing or on or after treatment start date, then the AE will be classified as Post-Randomization and On-treatment.

- Drug-Related AE: If the relationship is marked ‘Yes’ on the eCRF for an AE or the value is missing
- Post-Randomization and Post-Treatment last contact date for censoring (subjects not having AE) will be defined as the study completion date
- On-Treatment last contact date for censoring (subjects not having AE) will be defined as follows:
 - Day after treatment stop date (treatment stop date + 1) for subjects not having On-Treatment AE and continuing on study past (treatment stop date + 1)
 - Treatment stop date for all other subjects
- AE Person Years: (Cumulative total of time to AE for subjects who have the AE + Cumulative total of censoring time for subjects without the AE) / 365.25
 - For on-treatment adverse events, the start date of the person years value for each subject should be the treatment start date.
 - For post-randomization adverse events, the start date of the person years value for each subject should be the randomization date.
 - For post-treatment adverse events, the start date of the person years value for each subject should be the day after the treatment stop date (treatment stop date + 1).
 - If the AE onset date is completely missing, then impute the randomization date will be used for calculations of person years
- Incidence Rate (per 100 person years): (100 * Number of subjects with at least 1 AE) / AE person years
- For the analysis of the time to AE onset, if the AE onset date is missing then the time to AE onset will be counted as 1 day.

9.3.6. Laboratory Values

- If a laboratory value that is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. Examples: For 2 significant digits, '<x' becomes $x - 0.01$; for 1 significant digit, '>x' becomes $x + 0.1$; for 0 significant digits, '<x' becomes $x - 1$.
- If a laboratory value that is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with ' $\leq x$ ' or ' $\geq x$ ' is present, then the corresponding numeric value will be set equal to x.
- If there is more than one laboratory value on the same date for the same laboratory test, then the laboratory values associated with scheduled visits will be used.
- The following will be used to convert laboratory values from SI units to conventional units [Iverson, 2007]:
 - Triglycerides: Divide the mmol/L value by 0.0113 to get the mg/dL value.
 - Total cholesterol, LDL and HDL: Divide the mmol/L value by 0.0259 to get the mg/dL value.
 - Glucose: Divide the mmol/L value by 0.0555 to get the mg/dL value.
 - eGFR: Multiply the mL/sec/1.73m² value by 60 to get the mL/min/1.73m²
 - ACR: Divide the mg/mmol value by 0.113 to get the mg/g value
 - Total Bilirubin: Divide the μ mol/L value by 17.104 to get the mg/dL value
 - Serum Creatinine: Divide the μ mol/L value by 88.4 to get the mg/dL value
 - Calcium: Multiply the mmol/L value by 4 to get the mg/dL value

9.3.7. Efficacy Endpoints

9.3.7.1. Dates for Investigator Reported Efficacy Endpoints

Event dates for investigator reported efficacy endpoints are defined as the following based on the dates collected in the CRF:

- Death: date of death
- Myocardial infarction: Date and time of onset of symptoms that caused the subject to seek medical attention (If no symptoms, the presumed time of event onset)
- Stroke/TIA: Date and time of onset of neurological symptoms
- Coronary revascularization procedure: Date procedure performed

- Unstable angina: Date and time of onset of symptoms that caused the subject to seek medical attention (If no symptoms, the presumed time of event onset)
- Heart failure requiring hospitalization: date of event
- Limb amputation due to vascular cause: date procedure performed
- Non-coronary revascularization: date procedure performed
- Hospitalization for non-coronary ischemic event: date of hospitalization
- New onset diabetes: Diagnosis Date

There may also be specific instances where a subject experienced a fatal event due to stroke or MI and yet the direct cause of death is noted by the investigator to be due to something other than the fatal event. For instance, a subject may die within 30 days from complications of an MI and therefore the event is determined to be fatal. However, if the immediate cause of death was an infection, then the classification of death may be non-cardiovascular. In such instances, the time to the first fatal or non-fatal event (in these cases these cases due to stroke or MI) will be included in the composite endpoint. For the purpose of summarizing the components of major coronary events, MACE, or other composite endpoints the components will be displayed and the fatal event due to stroke or MI will be included with the non-fatal events and footnoted.

9.3.7.2. Dates for Adjudicated Efficacy Endpoints

Event dates for adjudicated efficacy endpoints are defined by the date of event provided by the adjudication committee:

- Death
- Myocardial infarction
- Stroke/TIA
- Hospitalization for unstable angina
- Heart failure requiring hospitalization

The date of urgent coronary revascularization for myocardial ischemia will be the adjudicated date of the hospitalization for unstable angina. For analyses of time to any coronary revascularization, the date of the revascularization procedure will be used. Note that because the CEC does not adjudicate the date of any revascularization procedures, these analyses will always utilize the investigator-reported dates for the procedure.

Because of the way the CRF is designed, a fatal MI is reported as both an MI and a death. Therefore, the fatal MI event could have an event date that differs from the death date because the subject may have died as a result of the MI but not on the very same day. For analysis of first occurrence major coronary events, MACE, MI, or any composite endpoint that includes both MI and death, the MI date will be used as the event date. For analysis of CHD death only, CV death only, and all-cause mortality only, the death date will be used. Similarly, for HUA with an outcome of death the date of HUA will be used for endpoints that include HUA and date of death for analysis of death.

Similarly, fatal stroke events are reported as both a stroke and a death. For analysis of first occurrence MACE, stroke, or any other composite endpoint that includes stroke and death, the stroke date will be used as the event date. For analysis of CV death only and all-cause mortality only, the death date will be used.

In the situation that there are any cases of a fatal MI (or fatal stroke) that does not have both an MI (or stroke) endpoint and a death endpoint reported, then the date of the event that is reported will be used in the analysis of all relevant endpoints. This would additionally apply to situations where the MI (or stroke) may occur within an analysis period and the death may occur outside of the analysis period; the endpoint with the date in the analysis period will be used for all relevant endpoints. There may also be specific instances where a subject experienced a fatal event due to stroke or MI and yet the direct cause of death is adjudicated to be due to something other than the fatal event. For instance, a subject may die within 30 days from complications of an MI and therefore the event is determined to be fatal. However, if the immediate cause of death was an infection, then the classification of death may be non-cardiovascular. In such instances, the time to the first fatal or non-fatal event (in these cases these cases due to stroke or MI) will be included in the composite endpoint. For the purpose of summarizing the components of major coronary events, MACE, or other composite endpoints the components will be displayed and the fatal event due to stroke or MI will be included with the non-fatal events and footnoted.

9.3.7.3. Missing or Partial Endpoint Dates

- If event dates are missing or partial and there is not sufficient information to classify the time period of the event, the event will be classified as occurring on-treatment and post-randomization. The event will also be considered to have occurred during the follow-up for cardiovascular events as defined in Section [9.3.7.5](#).
- The following rules for missing or partial event dates for events other than death will be implemented as long as the imputed date is after the randomization date. If the imputed date is prior to the randomization date, then the date of randomization will be imputed for the event date.
 - If only the day of the month is missing, impute the first day of the month, (e.g., --MAR2007 would impute as 01MAR2007).
 - If the month and day of the month is missing, impute 01JAN, (e.g., -----2007 would impute as 01JAN2007).
 - If the year, month, and day of month are missing, impute the randomization date.
- The following rules for missing or partial death dates will be implemented as long as the imputed date is after the randomization date. If the imputed date is prior to the randomization date, then the date of randomization will be imputed for the death date.
 - The latest clinic or telephone visit, endpoint date (other than death), non-fatal AE or SAE date or date last known to be alive based on third party follow-up will be determined. If the year, month, and day of month of the death are missing then the death date will be imputed as the latest of these dates.

- If only the day of the month of death is missing, then impute the first of the month (e.g. –MAR2007 would impute as 01MAR2007). However, if this imputed date results in a date that is prior to the latest clinic or telephone visit, endpoint date (other than death), non-fatal AE or SAE date or date last known to be alive based on third party follow-up then impute the missing day of death as equal to this date instead. For example:
 - If –MAR2007 is given as the death date and there is a non-fatal MI on 08MAR2007 then the imputed date of death would be 08MAR2007 rather than 01MAR2007 such that the death is not before the non-fatal MI.
 - If –APR2007 is given as the death date and the latest date is a non-fatal MI on 08MAR2007 then the imputed date of death would be 01APR2007.
- If the month and day of the month of death are missing, then impute as 01JAN (e.g., ----2007 would impute as 01JAN2007). However, if this imputed date results in a date that is prior to the latest clinic or telephone visit, endpoint date (other than death), non-fatal AE or SAE or date last known to be alive based on third party follow-up then impute the missing month and day of death as equal to this date instead. For example:
 - If --2007 is given as the death date and the latest date is a non-fatal MI on 08MAR2007 then the imputed date of death would be 08MAR2007 rather than 01JAN2007 such that the death is not before the non-fatal MI.
 - If –2008 is given as the death date and the latest date is a non-fatal MI on 08MAR2007 then the imputed date of death would be 01JAN2008.
- For deaths that occur after subjects have prematurely withdrawn from the study, missing or partial dates will be imputed as specified above except if the imputation places the death prior to or on the premature withdrawal date. In this case, the death date will be imputed as the premature withdrawal date + 1 day.

9.3.7.4. General Definitions

- CV death includes all deaths indicated as cardiovascular (including fatal MI and fatal stroke events) as well as deaths of unknown cause
- CHD death includes the following death events: fatal MI, sudden death (witnessed/unwitnessed), arrhythmia, congestive heart failure/shock, or other cardiovascular death
- Coronary revascularizations are recorded by the investigator. If the investigator states that the revascularization is prompted by ischemic discomfort at rest (>10 min) during the same hospitalization or hospital transfer for purpose of coronary revascularization then the investigator is prompted to also complete the cardiac ischemic events (CIE) eCRF page.. Summaries and analyses of any coronary revascularization procedures (including any composite endpoints) therefore will include both investigator reported revascularizations as well as revascularizations which were associated with a CIE.
- Urgent coronary revascularization for myocardial ischemia is not defined by the investigator and is only defined by adjudication. Based on adjudication, a coronary

revascularization can also be assigned to be a non-urgent coronary revascularization or a revascularization for the treatment of an MI.

- Endpoints last assessable date = date endpoint information last assessed on study
 - For subjects who complete the study on IP, the study completion date
 - For subjects who complete the study after having discontinued from IP use the study completion date if this is associated with a subject contact (clinic or telephone visit) or date of death. If the study completion date is associated with a third party contact then use the latest date endpoint information was assessed by a third party.
 - For subjects who withdraw early from the study use the date of withdrawal if this is associated with a subject contact (clinic or telephone visit). If the date of withdrawal is associated with a third party contact then use the latest date endpoint information was assessed by a third party. If the date of withdrawal is not associated with either a subject contact or a third party contact, then use the latest date of either the subject's last contact or latest date endpoint information was assessed by a third party.
- Time-to-event (Days) = (Date of Event – Randomization date) + 1
- Censored Time (Days) = (Censoring Date – Randomization date) + 1
- Person Years = (Cumulative total of time to first event for subjects who have the event + Cumulative total of censoring time for subjects without the event) / 365.25
- Incidence Rate (per 100 person years) = (100 * Number of subjects with at least 1 event) / First event person years
- Absolute Rate Difference (per 100 person years) = Darapladib incidence rate (per 100 person years) – Placebo incidence rate (per 100 person years)

9.3.7.5. Time period for Follow-up of Cardiovascular Efficacy Endpoints

The period for capturing CV efficacy endpoints begins at the date of randomization. The follow-up period for CV efficacy endpoints will cease at a date dependent on the follow-up path that a subject takes through the study as follows:

- For all subjects who remain on IP through End-of-Treatment visit, use the End-of-Treatment visit date
- For all subjects who remain on IP until contacted about the End-of-Treatment visit, but do not attend the End-of-Treatment visit, use the (last IP stop date + 1) or if missing, the endpoints last assessable date.
- For all subjects who discontinue IP early, use the endpoints last assessable date

Any endpoints that occurred before the start of this time period are considered to be prior to the time period for follow-up of cardiovascular efficacy endpoints, and any endpoints that occurred after the end of this time period are considered to be post the time period for follow-up of cardiovascular efficacy endpoints.

9.3.7.6. Time Period for Vital Status

The period for capturing vital status begins at the date of randomization. The end of this time period is defined in the following manner:

- For all subjects known to have died: use the date of death.
- For all subjects who complete the study, use the study completion date (See Section 9.3.1).
- For all subjects who withdraw from the study, but vital status has been ascertained, *and are known to have not died*, use the date last known to be alive from the Survival eCRF form. If vital status has not been ascertained following study withdrawal, use the study withdrawal date.

Any endpoints that occurred before the start of this time period are considered to be prior to the time period for vital status, and any endpoints that occurred after the end of this time period are considered to be post the time period for vital status.

This time period will be used for the analysis of all-cause mortality. In addition, a sensitivity analysis for the analysis of all-cause mortality will be defined in which subjects who complete the study on IP are censored at the end-of-treatment visit (or last IP stop date + 1 if there is not an end-of-treatment visit) and subjects who complete the study off IP are censored at the study completion date.

9.3.7.7. Time Period for On-treatment Cardiovascular Efficacy Endpoints

The period for capturing on-treatment CV efficacy endpoints begins at randomization. The end of this time period is defined in the following manner:

- For subjects who did not take IP, use the date of randomization
- For subjects whose last IP stop date is missing and who took IP, use endpoints last assessable date
- For subjects continuing on study past last IP stop date, use (last IP stop date + 1)
- For subjects whose study withdrawal/completion date and last IP stop date are the same day, use date of study withdrawal/completion

If the censoring date as defined above for on-treatment CV efficacy endpoints is after the censoring date as defined for the primary analysis during the time period for follow-up of CV efficacy endpoints (Section 9.3.7.5), then use the censoring date for the primary analysis time period.

Any endpoints that occurred before the start of this time period are considered to be prior to the time period for on-treatment cardiovascular efficacy endpoints, and any endpoints that occurred after the end of this time period are considered to be post the time period for on-treatment cardiovascular efficacy endpoints.

9.3.7.8. Time Period for Post-randomization Cardiovascular Efficacy Endpoints

The period for capturing post-randomization CV efficacy endpoints begins at randomization. The end of this time period is the endpoints last assessable date, with the exception that if a death has been reported in the database after this time then the death will be included in the analysis.

Any endpoints that occurred before the start of this time period are considered to be prior to the time period for post-randomization cardiovascular efficacy endpoints, and any endpoints that occurred after the end of this time period are considered to be post the time period for post-randomization cardiovascular efficacy endpoints.

9.4. Assessment Windows

Data for continuous variables that are not related to time-to-event will be summarized according to the scheduled visit time period for which they were recorded in the eCRF.

Unscheduled assessments will not be slotted to a particular time point, but will remain as unscheduled if they are either summarized or listed unless otherwise specified.

9.5. Values of Clinical Concern

Laboratory values of clinical concern, also known as Threshold laboratory values, are defined in Section 18.1.

Threshold ranges for vital signs are provided in Section 18.2.

9.6. Study Endpoints

The events that constitute the clinical endpoints also meet the criteria for SAE : cardiovascular death, MI stroke, urgent coronary revascularization, hospitalization for unstable angina, and heart failure requiring hospitalization. SAEs that form part of the efficacy endpoints are not subject to expedited reporting, regardless of the “expectedness” or “relatedness” of the event. The proposed implementation follows:

SAE Reporting: All SAEs and clinical endpoints will be reported using the same type of form, which is an SAE form specifically adapted for an outcomes study. The form includes an extra question at the beginning of the page that asks the investigator to indicate whether any of a list of endpoints has occurred

- If the answer is “no”, the event is handled as a normal SAE, including the appropriate reporting procedures for Suspected Unexpected Serious Adverse Reactions (SUSARs)
- If the answer is “yes”, and the event is one of the six events that have been agreed as exempt from expedited reporting to regulatory authorities, it is not entered into OCEANS (the sponsor’s database and system for tracking, analysis, and reporting of adverse events), and is not subject to expedited reporting. The eCRF prompts the investigator to provide any additional information that would be required for the independent, blinded adjudication committee. The other three listed endpoints (limp

amputation, non-coronary revascularization and hospitalization for non-coronary ischemic events) are handled as per the first bullet above.

Once the event is adjudicated, if the adjudication committee says it is not a clinical endpoint *and the event is not an adjudicated cardiovascular death*, it becomes an SAE, and is subject to expedited reporting if the expedited reporting criteria are met. However, as the event was reported initially on the SAE form, the information needed to process the SAE is already available.

Reporting events in this way reduces expedited reporting of events related to the disease process under study and the associated unblinding. The sponsor anticipates that although clinical endpoints and other SAEs would be reported separately in the clinical study report, the same data elements that would be collected for SAEs would also be available to report for clinical endpoint.

10. STUDY POPULATION

All study population analyses will be performed on the All Randomized (ITT) population, unless otherwise stated. A subset of the study population analyses will also be performed on the Safety population. Because of the size of the database, data listings will not be provided unless specified otherwise.

10.1. Disposition of Subjects

The number of randomized subjects in the Safety, All Randomized (ITT), and relevant substudy populations will be summarized by treatment group.

The number and percentage of subjects completing the study, withdrawing early from the study, or discontinuing IP during the study, overall and by reason, will be summarized by treatment group. Subjects completing the study will be summarized separately by survival status. Summaries of study withdrawal and IP discontinuation will be provided in person years by treatment group and additionally by region and country.

A summary of subject status during the study will be provided overall and by treatment group which includes information on the number of subjects with each status: taking at least one dose of IP, discontinuing IP, follow-up status, premature withdrawal status, and survival status. A summary of the type of subject contact at each scheduled visit will also be provided overall and by treatment group. A summary of the total follow-up time and percentage of total follow-up time during time periods of the study will be provided overall and by treatment group (see Section 9.3.4 for definitions). A summary of the number of subjects with each type of end of study contact and the timing of this contact will be provided overall and by treatment group. Graphical summaries may also be provided to accompany these summaries.

The number and percentage of All Randomized (ITT) subjects who had at least one inclusion/exclusion criteria deviation will be provided by treatment group. The number and percentage of All Randomized (ITT) subjects will be summarized by investigator, country, and region for each treatment group.

Kaplan-Meier plots will be provided to summarize the time to study withdrawal and the time to IP withdrawal by treatment group.

Summaries will be provided to show the number and percentage of subjects within each treatment group for whom the treatment blind was broken. In addition, a listing will include the country, center identification (ID), subject ID, treatment start date, treatment end date, and duration of treatment until unblinding for whom the treatment blind was broken.

A listing will be provided which shows the randomized treatment group to which each subject was assigned.

A list of questions was added to all telephone contacts made with the subject that includes subject responses relating to endpoint events, AEs, serious AEs, cancer, allergic reactions, and cardiovascular diagnostic procedures. A summary of the responses to these questions will be provided overall and by treatment group for all contacts at which this form was available for completion within the CRF.

An updated informed consent was released in the latter half of 2012 while the study was ongoing. The subject status at the time of the review of the updated informed consent along with the resulting subject decision regarding continuation of IP for those subjects on IP at the time of review of this updated informed consent will be summarized overall and by treatment group.

10.1.1. Inclusion/Exclusion Criteria

Protocol Amendment 1 made the following changes/clarifications to inclusion/exclusion criteria:

Inclusion Criterion 2:
(Change) **Original Protocol:** Male or female aged at least 18 years, inclusive, at randomization
Amendment 1: Male or female aged at least 18 years, inclusive, at randomization. In Taiwan, subjects must be aged at least 20 years, inclusive, at randomization

Exclusion Criterion 2: **Original Protocol:** Absence of obstructive coronary artery disease
(Clarification)

Amendment 1: Absence of obstructive coronary artery disease. (NOTE: If all stenoses are successfully treated by PCI, the patient is still eligible)

Exclusion Criterion 4: **Original Protocol:** Current liver disease, known hepatic biliary abnormalities or evidence of abnormal LFTs or other hepatic abnormalities
(Clarification)

Amendment 1: Cirrhosis, biliary abnormalities, unstable liver disease, evidence of abnormal LFTs or other hepatic

abnormalities that in the investigator's opinion would preclude the subject from the study

Exclusion Criterion 12:
(Clarification)

Original Protocol: Alcohol or drug abuse within the past 6 months, or current mental condition which may affect study conduct

Amendment 1: Alcohol or drug abuse within the past 6 months. Current mental condition (psychiatric disorder, senility or dementia), which may affect study compliance or prevent understanding of the study

Exclusion Criterion 14:
(Change)

Original Protocol: Lp-PLA2 activity =10 nmol/min/mL for subjects with both parents of Japanese, Chinese, or Korean ancestry

Amendment 1: Subjects with birth parents of at least 50% Japanese, Chinese or Korean ancestry must have Lp-PLA2 activity sample prior to randomization. If the value is <20 nmol/min/mL subject to be excluded'

For the purposes of reporting, text reflecting the latest protocol amendment language will be used, with appropriate footnoting which highlights that counts and percentages will reflect deviations from the then-current protocol version. E.g., a 19-year old Taiwanese randomized prior to publication of protocol amendment 1, would not be counted as a protocol deviation.

10.2. Protocol Deviations

The efficacy analyses will be performed on all subjects in the All Randomized (ITT) population, regardless of whether or not they had a protocol deviation. All major protocol deviations that may affect the integrity of the data that can be identified in the database will be summarized.

Major protocol deviations that may affect the integrity of the data are defined as the following:

- Failed to meet Inclusion Criteria 3, 4, or 5
- Met any of these Exclusion Criteria: 1, 2, 3, 4, 5, 6, 7, 8, 13, 14, or 15
- Evidence that subject who was randomized to IP did not take any IP
- Evidence that subject took the incorrect IP
- Overall IP compliance <80% or >120%
- Use of selected prohibited medications during the study while taking IP

Comments made in Section 10.1.1 regarding inclusion/exclusion criteria changes made during protocol amendments apply to this section as well.

Prohibited medications include chronic co-administration (>14 consecutive days) of IP with strong oral or injectable CYP3A4 inhibitors. Short-term administration (defined as ≤14 days) or topical administration of any duration is allowed and is not considered a protocol violation. Summaries of subjects who received any strong oral or injectable CYP3A4 inhibitors after randomization will be provided, with further summaries of those who took these medications with IP for ≤14 days or >14 days. Additionally, a summary of the type of CYP3A4 inhibitor medication will be provided for those who took these medications with IP for ≤14 days. A listing will be used to provide the CYP3A4 inhibitor medications that were co-administered with IP for >14 days. These summaries will be provided overall and by treatment group.

10.3. Demographic and Baseline Characteristics

10.3.1. Subject Demography

The following demographic and baseline characteristics will be summarized by treatment group. The number and percentage of subjects in each category will be provided unless specified otherwise:

- Age (display will provide summary statistics)
- Gender
- Ethnicity
- Race group
- FDA race group
- Tobacco use
- Country
- Region
- Body mass index (display will provide summary statistics)
- Systolic and diastolic blood pressure
- LDL-C (display will provide summary statistics)
- Lp-PLA₂ (display will provide summary statistics)

Additional summaries will be produced to summarize geographic ancestry data by treatment group.

Summaries of the number and percentage of subjects by treatment group will be provided for each level of each subgroup specified in Section 8.2. Box plots and bar charts may be produced to facilitate assessment of differences between treatment groups on baseline continuous and categorical endpoints, respectively.

10.3.2. Medical History/Detailed CV History

Information regarding patient's cardiovascular conditions as well as other relevant medical conditions is collected. These data will be summarized by number and percentage, overall and by treatment group as follows:

Qualifying Event

- Number of days between qualifying event and randomization (randomization date – qualifying event date)
- Qualifying event diagnosis (Unstable Angina/ Non ST Elevation MI (CK-MB or troponin > upper limit normal)/ ST Elevation MI)
- Qualifying ECG description (Persistent ST elevation ≥ 0.1 mV, Transient ST elevation ≥ 0.1 mV, dynamic horizontal/down-sloping depression ≥ 0.05 mV, Left bundle branch block, none of the above)
- Qualifying ECG collapsed categories (Transient ST elevation ≥ 0.1 mV OR dynamic horizontal/down-sloping depression ≥ 0.05 mV, Persistent ST elevation ≥ 0.1 mV OR Left bundle branch block, none of the above)
- Signs of heart failure at the time of hospital admission for qualifying event (yes/no)
- Number of days from QE to baseline PCI (PCI date – qualifying event date)

Qualifying Event Lab

- Troponin or CK-MB for qualifying event above upper limit of normal (yes/no)
- Assessment of left ventricular function closest to discharge (Normal, mild/moderate dysfunction $\geq 30\text{-}49\%$, Severe dysfunction $< 30\%$, Not done)

Medications at Time of Treatment for Qualifying Event

- Fibrinolytics (yes/no)

Cath Details (Baseline)

- Coronary angiography performed after qualifying event and prior to randomization (yes/no)
 - If yes, Number of vessels (including bypass grafts with $\geq 50\%$ stenosis (0, 1, 2, ≥ 3)
 - If yes, $\geq 50\%$ stenosis in the left main artery (yes/no)
- Number of days between coronary angiography and randomization (compute Randomization date – date of coronary angiography)

Note: negative values indicate that coronary angiography occurred after randomization

- Number and percent of patients with coronary angiography occurring after randomization

PCI Details (Baseline)

- PCI performed after qualifying event and prior to randomization (yes/no)
- Number of days between PCI and randomization (compute Randomization date – PCI date .
Note: negative values indicate that PCI occurred after randomization)
- Number and percent of patients with PCI occurring after randomization
- Vessel PCI performed on (Left main, left anterior descending, right coronary artery, left circumflex, bypass graft, ramus intermedium)
- Interventions (balloon angioplasty without stent, drug-eluting stent, bare-metal stent, atherectomy, other)
- Residual stenosis $\geq 50\%$ following PCI (yes/no)

Additional Predictors of Cardiovascular Risk Related to Inclusion Criteria 4

- a. Age ≥ 60 years at randomization (yes/no)
- b. History of document myocardial infarction prior to qualifying event (yes/no)
- c. Diabetes mellitus requiring pharmacotherapy (yes [Type I/Type II]/no [Diabetes mellitus not requiring pharmacotherapy/No diabetes mellitus])
- d. Significant renal dysfunction (eGFR ≥ 30 and ≤ 59 mL/min per 1.73 m^2) (yes/no)
- e. Polyvascular disease (yes/no)
 - Cerebrovascular disease
 - Carotid artery disease
 - Carotid artery stenting
 - Carotid artery surgery
 - Carotid artery stenosis
 - Prior ischemic stroke (> 3 months) Peripheral artery disease (yes/no)
 - Peripheral artery disease with stent or surgery
 - Peripheral arterial stenting
 - Peripheral artery disease with amputation
 - Peripheral artery disease requiring surgery other than amputation
 - Intermittent claudication
 - Ankle brachial index decreased (<0.9 in at least one ankle)
 - Number of additional predictors of CV risk (0, 1, 2, 3, 4, 5) i.e., counting the number of yes responses among a-e.

Other Cardiovascular Risks and Conditions of Interest

- Previous CABG (prior to qualifying event)
- Previous PCI (prior to qualifying event)
- Abdominal aortic aneurysm (yes/no)
- Angina pectoris (yes/no)
- Atrial arrhythmias (yes/no)
- Congestive heart failure (yes, NYHA Functional Class Code I-IV/ no)
- Hyperlipidemia (yes/no)
- Hypertension (yes/no)
- Moderate to severe valvular disease (yes/no)
- Prior TIA or stroke (yes/no):
 - Prior TIA
 - Prior Stroke

Other Medical Conditions and Items of Interest

- Asthma (yes/no)
- Chronic obstructive pulmonary disease (yes/no)
 - If yes: requiring oxygen therapy (yes/no)
- Sleep apnea (yes/no)
 - If yes: requiring non-invasive ventilation (yes/no)

Family History of Cardiovascular Risk Factors

- Family history of premature coronary heart disease (Male family member \leq 55 or female family member \leq 65) (yes/no)

History of Cancer

- History of Cancer (yes/no)(overall, and by primary site of cancer)
- History of adenomatous polyps of the small intestine or colon (yes/no)
- Family history of intestinal cancer (yes/no) (and broken out by small intestine and colon)
- Family history of adenomatous polyps (yes/no)

GI Conditions of Special Interest (if present at randomization)

- Crohn's disease (yes/no)

- Celiac disease (yes/no)
- Ulcerative colitis (yes/no)
- Familial adenomatous polyposis (yes/no)
- Peutz-Jegher's syndrome (yes/no)
- Hereditary non-polyposis colorectal cancer syndrome (yes/no)

10.3.3. Sleep Questionnaire

CV events have been directly associated with sleep apnea and overnight shift work, and inversely associated with habitual duration of sleep. To further investigate these associations, a paper copy of a questionnaire that assesses sleep habits and risk for sleep apnea (e.g., snoring, fatigue while awake, overnight shift work and average hours of sleep) will be given to subjects for completion at the Baseline Visit. Neck circumference, also directly associated with risk for sleep apnea, will be measured at the Baseline Visit.

Details regarding the planned analyses relating to the sleep questionnaire can be found in [Appendix 7](#).

10.4. Prior and Concomitant Medications

All medications will be coded using the GSK Drug Dictionary. A listing of the GSK Drug ATC Level 1, 2 and 3 and the Ingredient to which each verbatim term is coded will be provided.

Prior and concomitant medications are defined using the start date, the stop date, and ongoing fields recorded in the eCRF. See Section [9.3](#) for a summary of how missing dates are handled.

Medications can be described as pre-treatment, concomitant, and/or post-treatment. A pre-treatment medication is any medication taken during the interval extending up to the day prior to IP start. A concomitant (or synonymously, on-treatment) medication is any medication taken during the interval extending from IP start date to IP stop date + 1 day. A post-treatment medication is any medication taken after IP stop date + 1 day. All medications can be classified into one of 7 categories (pre-treatment only, concomitant only, post-treatment only, pre-treatment and concomitant, pre-treatment and post-treatment, concomitant and post-treatment, pre-treatment and concomitant and post-treatment). For subjects who did not take IP, all medications are considered pre-treatment.

Medications can also be described as pre-randomization and post-randomization. A pre-randomization medication is any medication taken during the interval extending up to the day prior to randomization. A post-randomization medication is any medication taken during the interval beginning on the day of randomization. All medications can be classified into one of 3 categories (pre-randomization, post-randomization, both).

Similarly, medications can also be described as those taken prior to and/or after the qualifying event (and similarly classified into one of 3 categories (medications taken prior to QE only, after QE only, both).

Medication Classifications are described graphically in [Figure 3](#). Examples that demonstrate programming flags are provided in [Table 5](#).

Figure 3 Medication Classification

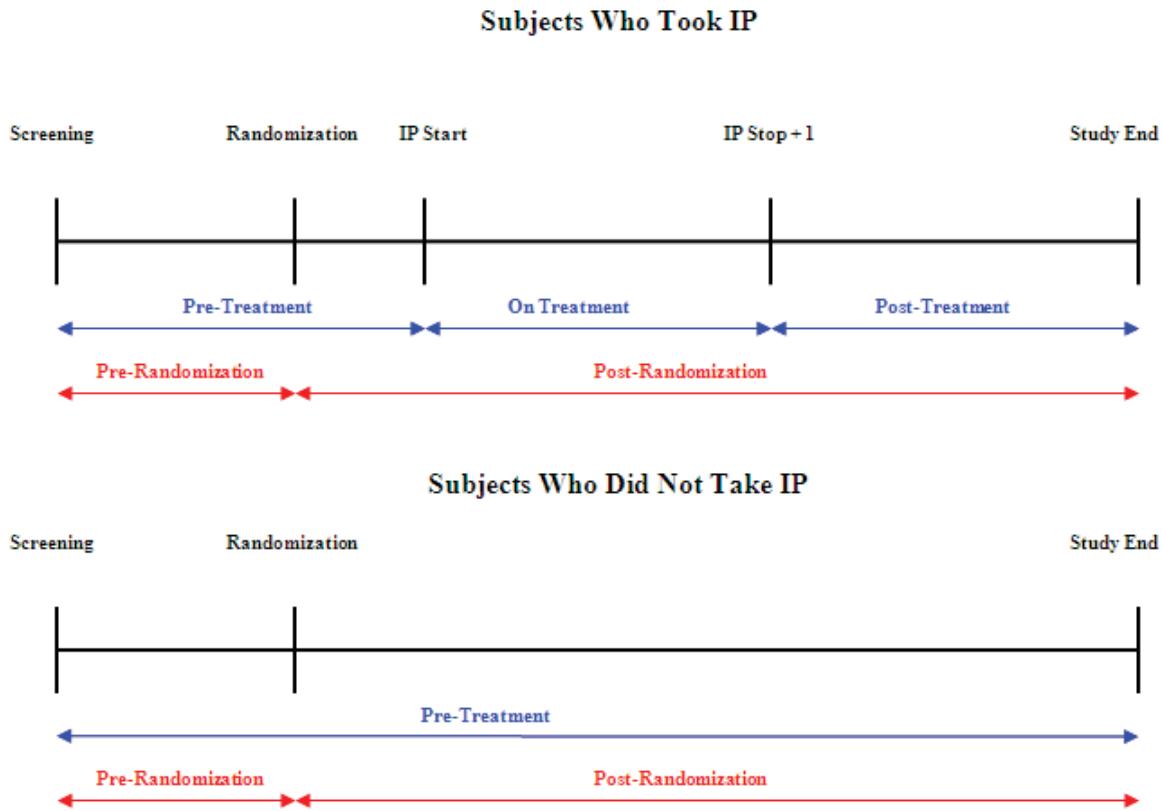


Table 5 Medication Classification Examples

Medication Intervals Examples			Treatment Flags		
Pre-Treatment	On-Treatment	Post-Treatment	Pre-Treatment	On-Treatment	Post-Treatment
X-----X			Y	N	N
X-----X			Y	Y	N
X-----X			Y	Y	Y
	X-----X		N	Y	N
	X-----X		N	Y	Y
		X-----X	N	N	Y
?-----X			Y	N	N
?-----X			Y ²	Y	N
?-----X			Y ²	Y ²	Y
X-----?			Y	Y ¹	Y
	X-----?		N	Y	Y
		X-----?	N	N	Y

x = randomization date or IP stop date

? = missing date

1. A medication that is started pre-treatment or on-treatment and has no stop date will be assumed to be ongoing for the remainder of the study.
2. A medication that is stopped on-treatment or post-treatment and has no start date recorded will be assumed to have been ongoing from the pre-treatment phase.

The number and percentage of subjects reporting the use of each concomitant medication will be summarized by treatment group, ATC Level 1, 2, and 3 (both with and without Ingredient). Summaries of the pre-treatment, on-treatment, post-treatment, and post-randomization medications will be provided separately. Additional summaries may also be provided for subgroups of medications used for particular therapeutic areas, including cardiovascular medications and medications used to treat diabetes.

At the Baseline visit and at other times throughout the study, further detail will be collected on medications that are considered standard of care for patients with CHD. Summaries of these specific standard of care medications will be presented by number and percentage of subjects for each response to each question on the standard of care medications eCRF page, summarized by treatment group and overall at baseline and at the nominal visit at which this additional information is collected. These summaries will also be produced by country and region.

10.5. Treatment Compliance

Treatment compliance, calculated as described in Section 9.3, will be based on the total number of tablets dispensed, the total number of tablets returned, and the total number of tablets taken for each container of IP assigned to a subject. Compliance will also account for the number of days between visits and the time the Investigator may have stopped a subject from taking IP temporarily between visits. Any container that has incomplete information (e.g., not returned, hence missing number of tablets returned or taken) will not be used in the calculation of treatment compliance. Treatment compliance will not be calculated for subjects missing information from more than 50% of their IP containers. Study compliance will be calculated similarly but will use the total days the subject was on study, regardless of the date the subject stopped taking IP (see Section 9.3).

Both treatment compliance and study compliance will be summarized using mean, standard deviation, minimum, median, maximum, and other appropriate percentiles by treatment group. Categories of compliance using number and percentage of subjects by treatment group will also be used to summarize treatment compliance and study compliance using the following categories: missing, <80%, 80-120%, >120%. Additional categories of treatment compliance will be summarized by treatment group: missing, <90%, 90-110%, >110% and ≤100%, >100%.

Summaries will be provided for compliance at scheduled visits using mean, standard deviation, minimum, median, maximum, and other appropriate percentiles by treatment group. Additionally, the following categories of compliance will be summarized by treatment group at scheduled visits: missing, <80%, 80-120%, >120%.

11. EFFICACY ANALYSES

Efficacy analyses will be based on the All Randomized (ITT) population, unless specified otherwise. Section 9.3.7.5 and Section 9.3.7.6, Section 9.3.7.7, and Section 9.3.7.8 describe subject level assessment windows used to identify events used in statistical analyses. Subjects who do not have the efficacy endpoint of interest will be censored at the end of the time period specified.

All efficacy analyses will compare darapladib to placebo. All statistical tests will be two-sided. Unadjusted p-values and 95% confidence intervals will be displayed where appropriate. Interpretation of statistical significance will reflect the statistical methodology appropriate for addressing the overall alpha level related to performing interim assessments as described in Section 4.1 and multiplicity related to testing multiple endpoints as described in Section 8.3.

11.1. Primary Efficacy Analysis

The primary endpoint is the time to the first occurrence of any component of the composite of major coronary events (CHD death, non-fatal MI, or urgent coronary revascularization for myocardial ischemia) as described in Section 2.2.1 and will include only events within in the follow-up for CV efficacy endpoints defined in Section 9.3.7.5.

11.1.1. Primary Analysis

The primary analysis, which will be based on major coronary events, will use only adjudicated events determined by the CEC.

Calculation of the time-to-event or censoring is described in further detail in Section 9.3.7.

First occurrence major coronary events for a subject is defined as the first event that occurs, determined by the event date, that is indicated as a CHD death, MI or urgent coronary revascularization for myocardial ischemia with further details in Section 9.3.7.2.

A summary of the number and percentage of subjects having major coronary events will be provided. The number and percentage of the type of first occurrence will also be provided for the components of major coronary events which is composed of CHD death, MI (fatal and non-fatal), and urgent coronary revascularization for myocardial ischemia. Additionally, summaries will include the number of events (including first and subsequent major coronary events) by type of event and the rate per 100 person-years.

Summaries of CHD death will include the number and percentage of subjects by cause of death

- CV Death due to coronary heart disease (CHD) (Sudden cardiac death (includes unwitnessed death of unknown origin), Death to an acute MI, Death due to HF or cardiogenic shock in patient with known CHD, Death from documented lethal arrhythmia (e.g., VF, VT etc) without known 2^o cause).

Summaries of MI will include the number and percentage of subjects by outcome of MI by

- Fatal or non-fatal
- Protocol-specified classification (Spontaneous MI in patient with no recent revascularization or biomarker elevation, Spontaneous MI in patient in whom biomarkers from a recent MI remain elevated, MI \leq 24h post PCI, MI \leq 72h post CABG, Pathological findings of an acute MI in patient with no recent revascularization and before biomarkers are available to confirm diagnosis, Silent MI diagnosed post-randomization)
- Joint ESC/ACCF/AHA/WHF Task Force recommendations for the Redefinition of Myocardial Infarction ([Thygesen](#), 2007): (Type 1,2, 3, 4a, 4b, 5)
- STEMI/NSTEMI

These detailed summaries of CHD death, MI, and urgent coronary revascularization for myocardial ischemia will be provided for all major coronary events and additionally for only first occurrence major coronary events.

Time-to-event analysis will be performed on the time to first occurrence of major coronary events using a Cox proportional hazards regression model with treatment group as the only covariate. The effect of treatment will be estimated using the hazard ratio, the corresponding confidence interval specified by the alpha-spending function, and its nominal 95% confidence interval. A p-value based on this model will be provided, and it will be assessed at the appropriate alpha level as specified in Section 4.1. The number and percentage of subjects with a major coronary event and the number censored at the end of the study will be displayed along with the results of the Cox proportional hazards regression model. A Kaplan-Meier survival curve will be created to provide a graphical display of time to major coronary event by treatment group. The Cox proportional hazards p-value will be used as primary; the log-rank test will be provided as a supportive analysis in the case where the proportional hazards assumption is reasonable and the primary analysis otherwise.

Confidence intervals for the rate per 100 person-years will also be reported. For within-group rates, the 95% confidence interval will be obtained using an exact Poisson method (Proc StatXact). For differences in rates between treatments, the 95% confidence interval will be constructed with a Normal approximation using Wald's method [[Liu](#), 2006]

To inform on the validity of the adjusted Cox proportional hazards model, the proportional hazards assumption will be assessed by plotting the logarithm of the negative logarithm of the estimated survivor function against the logarithm of time, for each treatment group. If the hazards are proportional, the lines should be approximately parallel.

A summary of the reason for censoring of subjects in the primary analysis of first occurrence major coronary events will be provided overall and by treatment group along with the corresponding total possible endpoint follow-up time, actual endpoint follow-up time and a percentage of the actual endpoint follow-up time compared to the total possible endpoint follow-up time. The actual endpoint follow-up time begins at a subject's randomization date and ends at either the primary endpoint first occurrence major coronary events date or for censored subjects the censoring date for the time period for CV efficacy endpoints (see Section 9.3.7.5). The total possible endpoint follow-up time begins at a subject's randomization date and ends at the subject's primary endpoint first occurrence major coronary events date or for censored subjects one of the following: the censoring date for the time period for follow-up of CV efficacy endpoints for subjects whose censoring date is on or after the beginning of the end of study window, the date of death for subjects who have died while in study, or the date of the middle of the end of study window for subjects whose censoring date is before the beginning of the end of study window.

Subgroup analysis will be performed for the subgroups of interest selected from those specified in Section 8.2 using a Cox proportional hazards model adjusting for treatment, the subgroup of interest, and a subgroup by treatment interaction. The hazard ratio and nominal 95% confidence interval for the treatment effect for major coronary events will be provided for each subgroup level for which analysis is performed. A forest plot will visually display the results of these analyses for the subgroup levels of interest. For those subgroups where the subgroup by treatment interaction is not significant at the 0.10 level, the model will be re-run removing this interaction to assess the significance of the subgroup effect without the interaction term in the model.

A supportive Cox proportional hazards model will be used to provide an adjusted hazard ratio and 95% confidence interval for major coronary events, adjusting for treatment and significant covariates (as identified in Section 8.2). This model will result from a backwards regression model. Initially all variables identified as significant at the 0.10 level through the analyses described in the previous paragraph will be considered for inclusion in the regression model. If the subgroup by treatment interaction is significant at the 0.10 level, then the interaction and the subgroup will be included in this model. The final model will retain all variables or interactions with treatment that remain significant at the 0.05 level following backwards regression variable selection. The subgroup main effect will be forced into the model if the subgroup by treatment interaction is significant at the 0.05 level. After this selection process has completed, interactions between treatment and the covariates will be assessed for inclusion in this model if qualitatively meaningful. Other models may be used to examine the robustness of this covariate adjusted model.

11.1.2. Sensitivity Analyses

Sensitivity analyses of the primary efficacy endpoint major coronary events will assess the robustness of the primary results. A nominal 5% significance level will be used. The structure of these analyses will be identical to the structure described for the primary efficacy endpoint. The following endpoints will be used for these purposes:

- The time to the first occurrence of on-treatment adjudicated major coronary events (excluding those major coronary events occurring after subjects permanently discontinued IP). This analysis will use the time period for on-treatment CV efficacy endpoints as described in Section 9.3.7.7.
- The time to the first occurrence of major coronary events as reported by the investigator (i.e., pre-adjudication), including only events occurring within the time period for follow-up of CV efficacy endpoints as described in Section 9.3.7.5.
- An analysis of all first occurrence major coronary events (including all efficacy endpoints occurring in the time period for post-randomization CV efficacy endpoints as defined in Section 9.3.7.8). Adjudicated data will be used wherever available; otherwise investigator reported data will be used.

Summaries of major coronary events by the time period of occurrence during the study will be provided by treatment group.

11.1.2.1. Sensitivity Analysis Accounting for Missing Data Associated with Prematurely Withdrawn Subjects

A sensitivity analysis will be conducted to explore the robustness of the primary analysis to different assumptions regarding primary endpoint status for subjects who withdraw from the study prior to experiencing the primary endpoint during the time period for follow-up of CV efficacy endpoints. This analysis will require use of simulations to impute data for these subjects during the unobserved time between the time subjects withdrew from the study and the end of the study (defined as the middle of the end of study window).

A simulation iteration will consist of

- imputing either a time to first occurrence major coronary event or a censoring time for each subject who withdrew from the study prior to experiencing a major coronary event based on a random observation from a piecewise exponential model allowing for breaks at 3m, 6m, 12m and 24m associated with the subject's treatment group
- analyzing the observed data from all subjects who completed the study and these imputed times for subjects who withdrew from the study using a Cox proportional hazards model with treatment as the only covariate
- retaining the resulting hazard ratio for the treatment effect from this Cox proportional hazards model.

A simulation scenario will consider a particular combination of an annualized placebo event rate and a hazard ratio for the treatment effect when imputing times for those who withdrew from the study prior to experiencing the primary endpoint. The distribution of the resulting hazard ratio from each individual simulation iteration will be summarized over 500 iterations.

The simulation exercise will consist of the following scenarios, where the observed annualized placebo event rate (r_p) and the observed hazard ratio for treatment effect (λ_o) are obtained from the model used for the primary endpoint.

- Annualized placebo event rate: r_p , $1.5*r_p$, $2*r_p$
- Hazard ratio for treatment effect: λ_o , 1, 1.2

A simulation exercise will be conducted using R Version 2.15 or higher to explore the robustness of the primary analysis to scenarios envisaged for subjects who withdraw prior to experiencing the primary endpoint.

For the placebo treatment arm, the time to primary endpoint, among those who have either not withdrawn or have experienced a 1st major coronary event prior to withdrawal, will be fit to a piecewise exponential distribution allowing for multiple breaks at 3m, 6m, 12m and 24m

As an example, assume that the protocol's assumption of annualized placebo event rates of 7.5% in the first year and 3.5% thereafter (i.e., only a single break at 12m). Further let's treat the hypothesized HR of 0.845 as observed. The resultant simulation exercise would consider:

Table 6 Example of Computed Annualized Darapladib Event Rates

Hazard Ratio for Darapladib vs. Placebo	Annualized Placebo Event Rate		
	$r_p=(7.5\%, 3.5\%)$	$2.5*r_p=(18.75\%, 8.75\%)$	$5*r_p=(37.5\%, 17.5\%)$
$\lambda_o=0.845$	(6.34%, 2.96%)	(15.84%, 7.40%)	(31.90%, 15.00%)
1	(7.5%, 3.5%)	(18.75%, 8.75%)	(37.5%, 17.5%)
1.2	(9.0%, 4.2%)	(22.5%, 10.5%)	(45.0%, 21.0%)

11.1.2.2. Data Handling for Centres with Questionable Data Integrity

In 2011, an audit was conducted on Centre 72515 resulting in closure of the site. As a result, the following action will be taken:

- A sensitivity analysis of the primary endpoint will be conducted excluding the 49 subjects randomized at Centre 72515.

Despite the audit summary characterizing the data as unreliable, the sponsor's position to include data from Centre 72515 in the primary and safety analyses is consistent with the data handling conventions described in Section 9 and stems from the ITT principal. The rationale for this is two-fold: (1) the existence of the patients randomized at this centre is verifiable, and (2) despite the lack of documentation that the patients met the protocol inclusion criteria, they were verified to have presented with an ACS event, hence being consistent with the disease under study in the protocol.

11.2. Secondary and Other Endpoint Efficacy Analyses

Secondary and other efficacy endpoints include those described in Section 2.2.2. Testing of these endpoints will follow the multiplicity strategy outlined in Section 4.1 and Section 8.3. See Section 18.3 for a graphical depiction of the efficacy endpoint testing strategy.

Analyses of the following endpoints will be performed in a manner identical to that described for the primary efficacy endpoint. All time-to-event secondary endpoints will follow the analysis strategy described for the primary endpoint of major coronary events. Analysis will include only those events occurring within the time period for follow-up of CV efficacy endpoints as described in Section 9.3.7.5, with the exception of the all-cause mortality only analysis which will include those events occurring during the time period for vital status as described in Section 9.3.7.6. For those endpoints or components of endpoints intended to go through the adjudication process per Section 2.2, only adjudicated results will be used. For other endpoints, investigator reported results will be used. Death events are reported by the investigator so that the CEC can confirm the cause of death as CV or non-CV, therefore all-cause mortality is considered an investigator-reported endpoint. Subgroup analyses and adjusted analyses as specified for the primary analysis may not be performed for the secondary and other endpoints. The number and percentage of subjects experiencing each endpoint will be provided. A Cox proportional hazards model will be used to compare treatment groups, yielding a hazard ratio and a corresponding 95% confidence interval. Kaplan-Meier survival curves will display the time to each of these endpoints. All analyses will be performed using the All Randomized (ITT) population. Section 9.3.7.5 and Section 9.3.7.6 describe subject level assessment windows used to identify events used in statistical analyses. A summary of all secondary and other efficacy endpoints by the time period of occurrence during the study will be provided by treatment group.

Summaries of death will include the number and percentage of subjects by cause of death

- CV Death due to coronary heart disease (CHD) (Sudden cardiac death (includes unwitnessed death of unknown origin), Death to an acute MI, Death due to HF or cardiogenic shock in patient with known CHD, Death from documented lethal arrhythmia (e.g., VF, VT etc) without known 2^o cause).
- CV Death not directly due to coronary heart disease (CHD) (Death due to cerebrovascular event, Death from pulmonary embolism, Death from complication of peripheral arterial disease or complication of cardiovascular procedure)
- Non-CV Death (Hemorrhage, Neoplasm / cancer, Trauma, infection / Sepsis, Post non-CV surgery, Pulmonary, Suicide, Other)

Summaries of stroke will include the number and percentage of subjects by outcome of stroke by

- Fatal or non-fatal
- Type of stroke (Ischemic, Hemorrhagic (intraparenchymal only), Ischemic with hemorrhagic conversion)

The following is a list of time-to-event endpoints:

- First occurrence of MACE
- First occurrence of total coronary events
- CHD death
- CV death
- First occurrence of MI (fatal and non-fatal)
- First occurrence of stroke (fatal and non-fatal)
- First occurrence of composite all-cause mortality, non-fatal MI, or non-fatal stroke
- First occurrence of the composite of CHD death and non-fatal MI
- All-cause mortality
- First occurrence of urgent coronary revascularization for myocardial ischemia
- First occurrence of heart failure requiring hospitalization
- First occurrence of total vascular events
- First occurrence of composite of total coronary events, excluding target lesion revascularization in subjects treated with PCI prior to randomization
- First occurrence of any coronary revascularizations excluding those planned prior to randomization
- New onset diabetes mellitus

For the endpoint of MACE the following analyses will be conducted in a manner similar to that of major coronary events:

- Subgroup analyses
- Sensitivity analyses
- Supportive Cox proportional hazards models in order to provide an adjusted hazard ratio and 95% confidence intervals

Additional efficacy endpoints are the time to first and subsequent major coronary events and time to first and subsequent MACE. The Prentice, Williams, Peterson (PWP) model [Prentice, 1981], based on the Cox proportional hazards model will be used to analyze these multiple event data. This model analyzes the first, second, etc. events while accounting for the correlation of events within an individual subject. Subjects are at risk for a k^{th} event only if they survived a $(k - 1)^{\text{st}}$ event. For all models described below, if there are not at least 15 k^{th} events per arm, the treatment effect associated with the k^{th} , $(k+1)^{\text{st}}$, etc. events will not be estimated. E.g., if arms 1 and 2 have only 7 and 16 subjects with four events, respectively then the models will only include terms for treatment effects on time to 1st, 2nd and 3rd events. Also, all event times will be relative to randomization, as opposed to intra-event time. I.e., *total times* rather than *gap times* will be used.

Three models will be conducted to provide hazard ratios, 95% CIs and p-values associated with treatment effects for both major coronary events and MACE. The first model will estimate a common treatment effect, regardless of the number of events experienced by subjects. A second model will be run that allows the treatment effects to differ depending on the number of events experienced by subjects. A third model will be run that allows the treatment effect associated with the time to 1st major coronary event/MACE to differ from a common treatment effect estimated for time to 2nd, 3rd, 4th, etc., major coronary event/MACE. The common treatment effect associated with the time to 2nd, 3rd, 4th, etc. in the third model would provide support for a treatment effect on time to subsequent major coronary event/MACE. It is possible for a patient to die in conjunction with experiencing a series of events in a short time frame. Ultimately, the CEC will identify the primary cause of death. For the purposes of recurrent event analyses, only those event occurring prior to and including the ‘fatal’ event will be included. If an event is determined to be fatal and the cause of death is adjudicated to be due to that fatal event, then only the first event will be counted and the death will not be considered a “recurrent” event but if the cause of death is a different cause then both the fatal event and the death would be counted. Additionally, suppose a subject has an MI, followed by a stroke, and dies within a short time frame. If the CEC attributes the death to the MI, only the MI will be used in the analysis. If the CEC attributes the death to the stroke, both the MI and stroke would be included. If the CEC attributes the death to some CV cause other than the MI and stroke, all three events would be used. The incidence of major coronary events and MACE experienced during the study (both on-treatment and off-treatment) will be summarized by treatment group. A chi-square test will be used to provide a supportive p-value for the comparison between treatment groups for the distribution of the incidence of major coronary events and MACE. Additionally listings of subjects who have a first and subsequent major coronary event or first and subsequent MACE will be provided with information on the type of major coronary events or MACE that occurred.

Additionally, a sensitivity analysis of first and subsequent major coronary events will be conducted using a negative binomial approach.

11.3. Other Efficacy Analyses

11.3.1. Other Time-to-Event Endpoint Analyses

Additional efficacy analyses may be performed to support the primary and key secondary analyses. Tables will be created that partition the investigator reported events as (adjudicated to the same event, adjudicated to a different event, adjudicated as a non-event). Summaries of investigator/adjudicator agreement by type of event reported by investigators may also be reported. Funnel plots will be provided for major coronary events and other key secondary endpoints by region.

An analysis of all (first and subsequent) total coronary events will be performed in a manner similar to the analysis for all major coronary events (first and subsequent), using the PWP model. Exploratory Analyses Related to Sleep Apnea and the Sleep Questionnaire

The sleep questionnaire responses and neck circumference measurements will be evaluated for the association of baseline sleep habits and risk for sleep apnea with the risk of future CV events and outcomes. A detailed analysis plan is provided in [Appendix 7](#).

11.3.2. Other Analyses

Summaries and analysis involving Lp-PLA₂ activity are described in Section [14.2](#).

Summaries and analysis of health care resources utilization are described in Section [13](#).

Efficacy analyses related to substudies and investigations can be found in detail in the appropriate appendices.

12. SAFETY ANALYSES

Safety analyses will be performed using the safety population.

12.1. Extent of Exposure and Treatment Duration

Treatment duration in days will be calculated as described in Section [9.3](#), using the first treatment start date and the last treatment stop date. IP exposure in days will be calculated for each subject using the treatment duration and then subtracting the number of days that the Investigator temporarily stopped a subject from taking IP during the study.

Treatment duration and exposure to IP will be summarized using mean, standard deviation, minimum, median, maximum, and other appropriate percentiles by treatment group. A cumulative distribution graphical summary of treatment duration and exposure to IP over time by treatment group will be provided. Summaries of exposure to IP will be provided in person years by treatment group. Additionally, summaries of exposure may be provided by selected subgroups.

Both treatment duration and exposure will be summarized as number and percentage of subjects who had ≤ 6 months, $>6-\leq 12$ months, $>12-\leq 18$ months, etc.

Summaries will be provided for subjects who have taken the incorrect IP during the study. The number and percentage of subjects taking incorrect IP and the tablet count of incorrect IP consumption will be provided along with a listing of these subjects.

Additional summaries for subjects who took the incorrect IP may be provided as needed.

12.2. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. A mapping of the MedDRA primary system organ class and preferred term to which each verbatim term has been coded will be provided in a listing.

AEs will be collected from the start of IP and until 35 ± 7 days after the final dose of IP or the Follow-up Visit, whichever is longer. SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study

participation (e.g., IP, 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 35 days after the final dose of IP or until the Follow-up Visit, whichever is longer. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.4.7 of the Protocol.

AE summaries will be provided overall and according to the investigator-identified endpoint status as specified below:

- All AEs, regardless of investigator-identified endpoint status
- AEs excluding those events identified by the investigator as endpoint events (These summaries would exclude those events reported by the investigator as CV death, MI, stroke/TIA, hospitalization for unstable angina, any coronary revascularization procedure, and hospitalization for heart failure. Note that deaths of unknown origin reported by the investigator will not be excluded from these AE summaries.)

Each AE will be categorized into periods according to its onset date. These periods are as follows: pre-randomization, post-randomization, pre-treatment, on-treatment, and post-treatment. An AE can be categorized into more than one period. Specifically, post-randomization AEs include both on-treatment AEs and post-treatment AEs. The exact definition of this categorization of an AE has been provided in Section 9.3.

The number, percentage, and rate per 100 person-years for subjects reporting at least one AE will be provided for each treatment group, using the first event person years as the reference time. These will be summarized by treatment group, primary system organ class, and preferred term. On-treatment, post-treatment, and post-randomization AEs will be summarized separately.

The most common AEs are defined as those occurring in at least 2% of the subjects within any treatment group. The number, percentage, and rate per 100 person-years for subjects reporting the most common post-randomization AEs will be summarized by preferred term and treatment group. The summary of most common AEs by treatment group will also be provided separately for AEs classified as on-treatment and post-treatment. A hazard ratio will be calculated for these most common AEs and a corresponding two-sided 95% confidence interval comparing darapladib versus placebo. The censoring time for the calculation of the hazard ratio is defined in Section 9.3.

Additionally, the most common AEs will be summarized graphically by preferred term and treatment group. The incidence rate in each treatment group and corresponding 95% confidence interval for the appropriate comparator estimate (e.g. odds ratio) of the darapladib group compared to the placebo group will be provided. Displays will be sorted by magnitude of risk, from largest to smallest. AE displays may include various types of estimates for comparison of treatment groups, which may include risk differences, odds ratios, risk ratios, and hazard ratios, as appropriate.

Subgroup summaries to assess the effect of subgroups (see Section 8.2) on the incidence of post-randomization AEs may be provided for select subgroup levels of importance by

treatment. Summaries of AEs may also be provided by selected treatment compliance categories.

The post-randomization AEs will be summarized by maximum intensity (mild, moderate, severe), treatment group, primary system organ class, and preferred term.

Post-randomization AEs the investigator presumes to be related to the study drug will be summarized separately by treatment, primary system organ class, and preferred term. Similar summaries will be provided for on-treatment and post-treatment AEs.

A listing of all AEs will be provided for subjects who were identified as taking any other investigational product during the study (other than the investigational product provided for this study).

Summaries of on-treatment AEs will be provided during the time period of co-administration of IP with strong oral or injectable CYP3A4 inhibitor medications. Additionally, separate summaries of on-treatment serious AEs will also be provided. These summaries will be generated overall and by treatment group for subjects with any duration of co-administration, for those with ≤ 14 days of co-administration, and for those with >14 days of co-administration. A listing of all fatal AEs during co-administration of IP with strong oral or injectable CYP3A4 medications will also be provided for those subjects with any duration of co-administration.

12.3. Deaths and Serious Adverse Events

The number, percentage, and rate per 100 person-years for subjects reporting each serious AE (SAE) will be reported by treatment group, primary system organ class, and preferred term. On-treatment and post-treatment SAEs will be summarized separately, as well as combined, as post-randomization SAEs. Additionally, the number, percentage, and rate per 100 person-years for subjects reporting each drug-related post-randomization, on-treatment, and post-treatment SAE will be reported by treatment group, primary system organ class, and preferred term.

The number, percentage, and rate per 100 person-years for subjects having a post-randomization fatal SAE will be reported by treatment group, primary system organ class, and preferred term. Similar summaries will be provided for on-treatment and post-treatment fatal SAEs. All fatal AEs will be provided in a listing.

12.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Subjects who permanently discontinue IP because of an AE should be followed until the study has ended. Subjects who withdraw consent will be followed in public records for vital status in conformity with the laws of their country of residence.

The number, percentage, and rate per 100 AE person-years for subjects reporting each post-randomization AE leading to discontinuation of IP and each AE leading to

withdrawal from the study will be summarized separately by treatment group, primary system organ class, and preferred term.

Adverse events of special interest are classified as follows:

- Abdominal pain
- Anaphylaxis
- Asthma
- Asthma-like
- Blood pressure
- Diarrhea
- Hypersensitivity Reaction
- Odor-related
 - Odor bathroom event (includes odor AEs related to feces or urine)
 - Odor non-bathroom event (includes odor AEs related to skin, hair, or smell)
 - Taste event
 - Breath event
- Other GI-related AEs (excluding Odor or Abdominal pain or Diarrhea AEs)

The preferred terms and verbatim text for post-randomization adverse events will be reviewed by the clinical group on an ongoing basis prior to unblinding. Terms for each special interest AE group will be identified. A listing will be provided to document the choice of terms within each group. In addition to reporting number and percentage of subjects having at least one occurrence, number of subjects by number of occurrence, the characteristics of the AE (serious, drug-related, etc.), outcome, maximum intensity, time to first onset, the duration of first, second, and third occurrence of the AE will be summarized by treatment group. For each count, a subject will be counted as follows:

- Serious/drug-related/leading to withdrawal/severe/fatal: If any specific AE falls in the respective category, the subject will be counted in that category.
- Outcome: The subject will be counted within a category if there is at least one specific AE in that category.
- Maximum intensity: The specific AE with the maximum intensity will be counted for this purpose. For example, a subject will be counted in the ‘severe’ category if there is at least one specific AE with severe intensity. A subject will be counted in ‘moderate’ category if there is at least one specific AE with moderate intensity and there is no specific AE with severe intensity.
- Time to first onset (days): The earliest of onset dates for the specific AE – treatment start date + 1

- Duration of the occurrence (days): AE resolution date – AE onset date + 1 for the occurrence.

If the AE onset date and/or resolution date is missing or incomplete in the database for any occurrence of the specific AE, time to first onset and/or duration of the first, second, and third occurrences will be left missing for the subject. These summaries of special interest AEs will be provided for those AEs classified as post-randomization, on-treatment, and post-treatment.

Kaplan-Meier plots may be produced for each special interest AE summarizing the time to the first occurrence of the special interest AE by treatment group.

A summary of the cumulative incidence of the special interest AEs by time of onset will also be provided for time of onset grouped into 6 month periods (<6 months, <12 months, etc. ...) by treatment group.

12.5. Pregnancies

Although pregnancies are not expected because of the inclusion criterion stating that female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy, a separate listing will include any pregnancy reported during the study.

Any complications of pregnancy for the mother or child, elective terminations for medical reasons, or spontaneous abortions will be summarized as stated in Section 12.2 for AEs or SAEs.

12.6. Clinical Laboratory Evaluations

At the Screening Visit, if local laboratory test results required for enrollment are not available, samples must be collected and sent to the central laboratory for assessment of all of the following: eGFR, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). In addition, subjects with both parents of Japanese, Chinese, or Korean ancestry must have a blood sample collected for assessment of Lp-PLA2 activity by the central laboratory prior to randomization; if eligible for study entry, Lp-PLA2 activity is not repeated at Baseline.

Dipsticks for protein in the urine will be used. If the dipstick is positive for protein, a urine sample will be sent to the central lab for assessment of ACR.

At the Baseline Visit, blood will be collected for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (third generation enzyme immunoassay) and sent to the central lab for analysis.

Blood will be collected at the times specified below for analysis at the central laboratory for the following safety labs:

- Clinical Chemistry (Baseline, Months 3, 6, 12, and every 6 months until study end, End of Treatment)

- Blood urea nitrogen
- Calcium
- Chloride
- Serum Creatinine
- eGFR
- Potassium
- Sodium
- Bicarbonate
- Hemoglobin subtype A1c (HbA1C), only in subjects with diabetes mellitus
- Fasting Plasma Glucose
- Fasting Lipids (Baseline, Months 3, 6, 12, and every 6 months until study end, End of Treatment)
 - Total cholesterol
 - LDL, Calculated for subjects with triglycerides \leq 400 mg/dL (4.52 mmol/L) or LDL, Direct for subjects with triglycerides $>$ 400 mg/dL (4.52 mmol/L). Note: Summaries of LDL will include either the LDL, calculated value (if available) or the LDL, direct value for a subject otherwise. LDL, calculated and LDL, direct summaries will not be provided separately.
 - HDL, Direct
 - Triglycerides
 - Non-HDL Cholesterol
- Liver Chemistry (Baseline, Months 3, 6, 12, and every 6 months until study end, End of Treatment)
 - Alkaline phosphatase
 - ALT
 - AST
 - Total Bilirubin
 - Total Protein
 - Serum Albumin
- Hematology (Baseline, Months 3, 6, 12, and every 6 months until study end, End of Treatment)
 - Hematocrit
 - Hemoglobin
 - Platelet Count

- White Blood Cells Count
- Neutrophil Count
- Urinalysis (Baseline, Month 6, and every 12 months until study end, End of Treatment):
 - Presence of protein

Assessment of ACR through central laboratory is only performed if urine is positive for protein on dipstick assessment. In addition to the visits listed for the laboratory assessments above, any of these assessments can be performed at an unscheduled/retest visit or at the follow-up visit at the discretion of the investigator.

Continuous variables will be summarized using mean, median, standard deviation, minimum, maximum, and other appropriate percentiles. Presence of blood or protein in the urine will be summarized as number and percentage of subjects at each visit by treatment group. Graphical summaries may also be provided.

For purposes of statistical analyses, the latest laboratory test value taken on or before the randomization date will be used as the baseline value. An end of treatment lab value will be defined per the end of treatment value definition in Section 9.3.1. All other laboratory assessments will be summarized according to the nominal scheduled visit at which they were taken. In the scheduled visit summary displays, any unscheduled/retest laboratory assessments will not be summarized in a nominal scheduled visit row, but they will be summarized in a row for all post baseline assessments. The parameters for all scheduled visits will be summarized by treatment group. Change from baseline for all post-baseline visits will also be summarized by treatment group. Additionally, summaries of the change from baseline at Month 3 and at the end of treatment visit (derived) along with a 95% confidence interval and p-value for both within treatment differences and between treatment differences will be provided. Graphical summaries may also be provided.

Laboratory analytes of interest may be summarized graphically.

All of the tabular summaries described above will include summaries in both SI units and conventional units for the following laboratory tests: total cholesterol, LDL (calculated and direct combined), HDL-direct, triglycerides, glucose, total bilirubin, serum creatinine, and calcium.

12.6.1. Abnormal Laboratory Values

Only those laboratory tests with a numeric laboratory normal range and those subjects with a baseline value and at least one post-baseline value will be used in these summaries.

Laboratory values within the testing laboratory's normal range are considered normal; those outside the normal range are considered abnormal. Laboratory values that are above the upper limit of the normal range are considered high abnormal; those that are below the lower limit of the normal range are considered low abnormal. The laboratory's normal range values are defined in Section 18.1.

The number and percentage of subjects who exhibit high abnormal or low abnormal values at any post-baseline visit will be summarized by treatment group and visit. Laboratory data transitions from baseline (low abnormal, normal, high abnormal) to post-baseline visits will be summarized by treatment group for each laboratory test. Laboratory data transitions from baseline to post-baseline visits will also be provided for eGFR according to the following categories: normal ($\geq 90 \text{ ml/min}/1.73\text{m}^2$), mild ($\geq 60 \text{ to } < 90 \text{ ml/min}/1.73\text{m}^2$), moderate ($\geq 30 \text{ to } < 60 \text{ ml/min}/1.73\text{m}^2$), and severe ($< 30 \text{ ml/min}/1.73\text{m}^2$)

Summaries may be produced for the rate per 100 person-years exposure for subjects with laboratory values outside the normal range.

12.6.2. Values of Clinical Concern (Threshold) Analysis

Displays of values of clinical concern will include only those laboratory tests with a numeric laboratory clinical concern range and those subjects with a baseline value.

The laboratory values of clinical concern (threshold laboratory values) are defined in Section 18.1. A laboratory value that is above the upper limit of the threshold range given in this table is considered a high threshold value. A laboratory value that is below the lower limit of the threshold range is considered a low threshold value.

The number and percentage of subjects who exhibit high threshold and low threshold values at any post-baseline visit will be summarized by treatment group and visit.

Shifts from non-threshold value at baseline to any threshold value at any post-baseline visit will be summarized by treatment group.

Summaries may be produced for the rate per 100 person-years exposure for subjects with laboratory values outside the clinical concern range.

12.6.3. Abnormal Liver Function Tests

Liver function tests (ALT, AST, Total Bilirubin, and Alkaline Phosphatase) will be graded according to the criteria provided by the FDA [FDA, 2007] with modifications to ensure that the grades are mutually exclusive. For consistency with previous darapladib studies which were aligned with the World Health Organization (WHO) and National Cancer Institute (NCI) recommendations [NCI, 2009; WHO, 2009], an additional set of grades will be assigned to these liver function tests. The liver function tests grading guidelines are summarized in Table 7..

Table 7 Liver Function Tests by Grade Expressed as N-fold Upper Limit Normal

Analyte	Grade 1	Grade 2	Grade 3	Grade 4	Grade 4b*	Grade 5
FDA Guidelines						
ALT	>1x - <3x	≥3x - ≤5x	>5x - ≤10x	>10x - ≤20x or ≥3x + Bilirubin ≥1.5x	>10x - ≤20x or ≥3x + Bilirubin ≥2x	>20x
AST	>1x - <3x	≥3x - ≤5x	>5x - ≤10x	>10x - ≤20x	n/a	>20x
Total Bilirubin	>1x - ≤1.5x	>1.5x - ≤2x	>2x - ≤5x	>5x - ≤10x	n/a	>10x
Alkaline Phosphatase	>1x - ≤1.5x	>1.5x - ≤3x	>3x - ≤5x	>5x - ≤10x	n/a	>10x
WHO and NCI Guidelines used in Previous Darapladib Studies						
ALT	>1x - <3x	≥3x - <5x	≥5x - <20x	≥20x or ≥3x + Bilirubin ≥1.5x	n/a	n/a
AST	>1x - <3x	≥3x - <5x	≥5 x - <20x	≥20x	n/a	n/a
Total Bilirubin	>1x - <1.5x	≥1.5x - <3x	≥3x - <10x	≥10x	n/a	n/a
Alkaline Phosphatase	>1x - <2x	≥2x - <5x	≥5x - <20x	≥20x	n/a	n/a

Note: n/a = not applicable

* Grade 4b is a subset of the Grade 4 definition.

Upper limit normal (ULN) is the upper limit of the normal clinical range (see Section 18.1).

The maximum toxicity grade recorded for each parameter at any post-baseline visit will be selected for each subject. The number and percentage of subjects with elevated liver function tests at any post-baseline visit will be presented by maximum toxicity grade. These tabular summaries will be provided separately for both the FDA grading system and the WHO/NCI grading system used in previous darapladib studies. Graphical summaries may also be provided.

12.6.4. Standard of Care Laboratory Goals

Subjects should be treated during the study using standard of care for CHD. This includes specific goals for laboratory measures consisting of LDL-C, fasting plasma glucose, and HbA1c for diabetics. Summaries will be provided at the baseline visit and at other times throughout the study when these lab values are assessed for the number and percentage of subjects reaching the standard of care laboratory goals as specified below. These summaries will also be provided by region and country. These thresholds may be modified, as appropriate, if the established standard of care is altered during the course of follow-up. Graphical summaries may also be provided.

- LDL-C: <70 mg/dL or <1.8 mmol/L
- LDL-C: <100 mg/dL or <2.6 mmol/L
- Glucose: <110 mg/dL or <6.1 mmol/L
- HbA1c for diabetics: <7%

12.7. Other Safety Measures

For purposes of statistical analyses, the latest measurement on or before the randomization date will be used as the baseline value for vital signs, body composition assessments and the Modified Rankin Scale. An end of treatment lab will be defined as per the end of treatment value definition in Section 9.3.1. All other assessments while on-treatment will be summarized by the nominal visit at which they were collected.

12.7.1. Vital Signs

Vital signs are collected by an automatic blood pressure measurement device and are the following:

- Systolic blood pressure [SBP] (Baseline and every clinic visit)
- Diastolic blood pressure [DBP] (Baseline and every clinic visit)
- Heart Rate (Baseline and every clinic visit)

The vital signs values will be summarized by treatment group for each visit at which they are collected. Change from baseline for each post-baseline assessment will also be summarized. Graphical summaries may also be provided.

Clinical concern (threshold) ranges for each of the vital signs have been established (see Section 18.2). The number and percentage of subjects who exhibit high threshold or low threshold values at any post-baseline assessment will be summarized by treatment group and visit.

A generalized estimating equations model will be used for the change from baseline in SBP, DBP, and heart rate with subject fitted as a repeated effect and terms included for treatment, visit, baseline value, treatment by visit, and baseline by visit interactions. An appropriate variance-covariance matrix will be used to model the correlation among visits within individual subjects. A point estimate and 95% confidence interval for the mean difference between darapladib and placebo subjects at Month 24 (primary) and other time points (secondary) will be produced based on this model. Graphical summaries may also be provided.

Change from baseline in systolic blood pressure at each visit will be categorized as follows: decrease \geq 30mmHg, decrease \geq 20mmHg and <30mmHg, decrease \geq 10mmHg and <20mmHg, decrease \geq 5mmHg and <10mmHg, no clinical change (decrease from baseline $>$ 5 mmHg and increase $<$ 5mmHg), increase \geq 5mmHg and < 10mmHg, increase \geq 10mmHg and <20 mmHg, increase \geq 20mmHg and <30 mmHg, and increase \geq 30mmHg.

Change from baseline in diastolic blood pressure at each visit will be categorized as follows: decrease ≥ 20 mmHg, decrease ≥ 10 mmHg and <20 mmHg, decrease ≥ 5 mmHg and <10 mmHg, no clinical change (decrease from baseline >5 mmHg and increase <5 mmHg), increase ≥ 5 mmHg and <10 mmHg, increase ≥ 10 mmHg and <20 mmHg, and increase ≥ 20 mmHg.

Heart rate at each visit will be categorized as follows: < 50 beats/min, ≥ 50 beats/min to ≤ 100 beats/min, and > 100 beats/min.

The number and percentage of subjects with change from baseline in blood pressure and at visit heart rate in each of the above categories will be summarized by treatment group and visit.

Subjects should be treated during the study using standard of care for CHD. This includes specific goals for blood pressure measurements. Summaries will be provided at the baseline visit and at other times throughout the study when these measurements are assessed for the number and percentage of subjects reaching the standard of care goals as specified below. These summaries will also be provided by region and country.

- Blood pressure for subjects without diabetes or chronic kidney disease: SBP <140 mmHg, DBP <90 mmHg
- Blood pressure for subjects with diabetes or chronic kidney disease: SBP <130 mmHg, DBP <80 mmHg
- Blood pressure for all subjects: SBP <140 mmHg and DBP <90 mmHg

12.7.2. Body Composition Assessments

Body composition assessments collected during the study are the following:

- Height (Baseline, Month 12 and every 12 months, End of Treatment)
- Weight (Baseline, Month 1, Month 3, Month 6 and every 6 months, End of Treatment)
- Body mass index [BMI] (Baseline, Month 1, Month 3, Month 6 and every 6 months, End of Treatment). Note: The calculation of BMI will use the weight value at the scheduled visit assessments for weight and will use the height at either the current visit (if measurement of height is scheduled at that visit) or the most recent previous height at a scheduled visit.
- Hip circumference (Baseline, Month 12 and every 12 months, End of Treatment)
- Waist circumference (Baseline, Month 12 and every 12 months, End of Treatment)
- Waist/Hip Ratio (Baseline, Month 12 and every 12 months, End of Treatment)

The body composition measures will be summarized by treatment group for each visit at which they are collected. Change from baseline for each post-baseline assessment will also be summarized when appropriate. Graphical summaries may also be provided.

A generalized estimating equations model will be used for the change from baseline in weight, BMI, and waist/hip ratio with subject fitted as a repeated effect and terms included for treatment, visit, baseline value, treatment by visit, and baseline by visit interactions. An appropriate variance-covariance matrix will be used to model the correlation among visits within individual subjects. A point estimate and 95% confidence interval for the mean difference between darapladib and placebo subjects at each time point will be produced based on this model. Graphical summaries may also be provided.

12.7.3. Other Assessments

The Modified Rankin Scale is scheduled to be collected at the Baseline visit and at every subsequent clinic visit during the study.

This measure will be summarized using number and percentage of subjects with each level of the Modified Rankin Scale by treatment group for each visit at which it is collected.

12.7.4. 12-lead ECG Assessments

For purposes of statistical analyses, the latest post-screening ECG measurement on or before the randomization date will be used as the baseline value. The end of treatment value will be defined as the last measurement on or prior to the treatment stop date. All other assessments while on-treatment will be summarized by the nominal visit at which they were collected.

These values will be summarized by treatment group for each visit at which they are collected. Change from baseline for each post-baseline assessment will also be summarized for continuous measures. The following is a list of ECG measures that are collected and reported by the local investigator:

- Heart rate
- PR interval
- QRS Duration
- Uncorrected QT interval
- Corrected QT (QTc) interval
- Result of ECG (at baseline visit: (normal, abnormal but not clinically significant, or abnormal and clinically significant))
- Change in ECG Result (post-baseline visits: No change or insignificant change from previous ECG and Clinically significant change from previous ECG)
- Findings

QTc intervals will also be calculated using Bazett's and Fredericia's formulas summarized below based on the heart rate and the uncorrected QT interval (QT). These QTc intervals will be summarized as stated above for other continuous measure obtained from ECG assessments.

- Bazett's QT interval = $QT / \sqrt{(60 / HeartRate)}$
- Fredericia's QT interval = $QT / (60 / HeartRate)^{1/3}$

Additionally, summaries associated with screening ECG taken in conjunction with the qualifying event will summarize the investigator's assessment as recorded in the eCRF. These will include number and percentages reporting

- ST-segment deviation during qualifying event (yes/no)
- PCI performed for qualifying event (yes/no)
- Catheterization performed for qualifying event (yes/no)

Tables may be repeated by Qualifying Event category and/or Troponin elevation status.

12.7.5. Cancer Diagnoses and GI Neoplasms/ GI Polyps

Limited data on medical history of cancer have been collected prior to randomization. Information on specific gastrointestinal (GI) conditions of special interest, including the date of diagnosis, have been collected since screening throughout the study. These conditions will be categorized as "present prior to randomization" and "diagnosed post-randomization" based on date of diagnosis (imputed if necessary according to the algorithm provided in Section 9.3.2). For summary of medical history of cancer and specific GI conditions present prior to randomization, please see Section 10.3.2 . For primary cancer location in subjects with cancer history prior to randomization, a list of GI location and Other location has been provided in Appendix 4, Section 18.4.1. Specific GI condition diagnosed post-randomization will be summarized by treatment.

Details of any new or recurrent/progression of cancer will be reported by the investigator in the cancer/GI neoplasm/polyp (CNP) form in the electronic case report form (eCRF) throughout the study (from randomization to the end of study), regardless of whether the subject was on IP at the time of diagnosis. Benign GI polyps, benign GI neoplasms or GI neoplasms unable to be determined as benign or malignant will also be recorded on the CNP form. The cancers that involve the GI tract/system (defined as the entire tract from the esophagus to rectum as well as the liver, biliary system/gall bladder and pancreas) or any GI polyp or other GI neoplasm (benign or of unknown pathology) will be sent for adjudication. Anal polyps or neoplasms, although not defined as being included in the GI tract/system, will also undergo adjudication to avoid misclassification

Malignant neoplasms at non-GI sites will be reported on the CNP form in the eCRF but will not be adjudicated (unless the neoplasm spreads to the GI system). If the investigator reports a benign neoplasm or a neoplasm unable to be determined as benign or malignant at a non-GI site, the data will remain in the database, but will not be included in the analysis of cancer data.

The cancer summaries will include only post-randomization reports of CNPs; if the date of diagnosis/procedure is before the randomization date, the record will not be included in the data summaries or analyses. If the date of event is completely missing or partially

provided, the algorithm for missing date imputation for CV endpoints other than death described in Section 9.3.7 will apply.

For any time-to-event analysis, for subjects who did not have cancer of interest, the study completion date (for definition, see Section 9.3.1) will be used as the censoring date.

12.7.5.1. All Cancers and/or Polyps/ GI Neoplasms (reported by Investigator only)

The number and percentage of subjects with any cancer – new, recurrence/progression – will be provided by treatment group. Primary site location for all cancer diagnoses will also be summarized by treatment group – classified as GI (sub-classified as small intestine, large intestine, small/large intestine – region unknown and GI excluding Small/large intestine) and Other locations (list provided in Appendix 4, Section 18.4.2), along with whether metastases were present and if yes, location of metastases. Cancers and/or polyps involving the GI system will be summarized, including characterization regarding whether localized to the GI system without spread, primary GI with metastases, or primary site location not GI but spread to GI.

Similar summaries will be provided separately for any new cancer and any recurrence/progression of cancer. Source of diagnosis date will be summarized by treatment group for these displays.

12.7.5.2. Cancers involving GI System and GI Polyps/ GI Neoplasms

Investigator-reported Events

For investigator reported cancers – new or recurrence/progression of cancer – which involve GI system will be summarized by treatment group and by source of diagnosis (e.g. pathological report, diagnostic procedure, symptoms, etc.), location of primary site as well as metastases status. Similar summaries will be provided separately for new cancers and recurrence/progression of cancer involving GI system.

The above summaries will be repeated for cancers with 1) GI as primary site; 2) small or large intestine as primary site. Small/large intestine sites are determined by GSK clinical review of codes admissible in the eCRF; the list is provided in Appendix 4, Section 18.4.2

Investigator reported benign GI polyps or GI neoplasm of unknown pathology will be summarized by treatment group; summary for location of polyp/neoplasm will also be provided.

Adjudicated Events

GI neoplasm cases including cancers that are sent to adjudication will be summarized for involving or not involving GI system as well as for cancer – new cancer, recurrence/progression of cancer, and polyp/neoplasm – benign or of unknown pathology. Number and percentage of subjects having either a GI cancer diagnosis or a GI growth of unknown pathology will be provided by treatment group. Some cases may

be adjudicated as not involving the GI system and/or not a cancer or neoplasm at all; these adjudication results will be summarized by treatment group.

For adjudicated CNP records, whether the cancer and/or polyp involves the GI system will be summarized by treatment group and types of primary GI, primary other than GI but metastases in GI, and ‘no known involvement in GI’. In addition, these summaries will be provided for new cancer and recurrence/progression of cancer separately. New and recurrence/progression of cancer with GI as primary site, and with small intestine or large intestine as primary site, will be summarized by treatment.

Adjudicated GI malignancy information for new cancer or recurrence/progression of cancer, will be summarized by treatment group – source of diagnosis, whether onset of malignancy is likely to be before randomization, extent of involvement (localized or metastasized) and tissue of origin with GI as primary site (also at the level of small intestine, large intestine, GI other than small/large intestine – list provided in [Appendix 4](#), Section [18.4.3](#)). In addition, this information will be provided for new cancers and recurrence/progression of cancers separately.

The hazard ratio using Cox proportional hazard model and associated 95% confidence interval comparing treatment group for any adjudicated GI malignancy, any adjudicated GI malignancy excluding those with evidence suggesting onset likely prior to randomization, any adjudicated new malignancy, any adjudicated recurrent/progression of cancer will be provided, including the p-value for significance of the hazard ratio. The Kaplan-Meier survival curves for time to cancer for each of these types will be provided, along with log-rank p-value to compare treatment group. Similar statistics will be provided for 1) adjudicated GI malignancies with GI as primary site; 2) adjudicated GI malignancies with the small or large intestine as primary site.

Adjudicated benign GI polyp/ GI neoplasm information will be summarized by treatment group for type and/or location; number and percentage of subjects reporting only one benign GI polyp/ GI neoplasm and those reporting multiple benign GI polyp/ GI neoplasm will also be provided by treatment. Only adenomatous GI polyps are classically considered to be neoplastic (including tubular, tubulovillous, villous and sessile serrated polyps) which have the potential of becoming malignant in future. In contrast, other polyp types (including, but not limited to, hyperplastic, inflammatory, hamartomatous, etc.) are considered non-neoplastic and are considered unlikely to become cancerous. The number and percentage of subjects with neoplastic and non-neoplastic benign polyps will be provided by treatment group.

Information for adjudicated neoplasm or polyp that are unknown to be benign or malignant will be summarized by treatment group for source of diagnosis, involvement of GI system and the location of growth.

Separate summaries of adjudicated GI malignancies - with the primary site in GI system and with the small intestine or large intestine as primary site – will be provided by treatment group with number and percentage of subjects in each baseline subgroup:

- Age at randomization: <65 years, 65-74 years, >=75 years

- History of cancer: Yes/No
- History of any GI condition of special interest: Yes/No
 - Crohn's disease (diagnosed prior to randomization): Yes/No
 - Celiac disease (diagnosed prior to randomization): Yes/No
 - Ulcerative colitis (diagnosed prior to randomization): Yes/No
 - Familial adenomatous polyph (diagnosed prior to randomization): Yes/No
 - Peutz-Jegher's syndrome (diagnosed prior to randomization): Yes/No
 - Hereditary non polyposis colorectal cancer syndrome (diagnosed prior to randomization): Yes/No
- History of adenomatous polyps of small intestine or colon prior to randomization: Yes/No
- Family history of intestinal cancer: Yes/No
 - Small intestine only
 - Large intestine only
 - Both small and large intestine
- Family history of adenomatous polyps: Yes/No
- History of GI cancer: Yes/No
 - (defined as: 'Yes' when History of cancer = Yes and any location of cancer is reported within GI system; 'No' if either history of cancer=No, or history of cancer = Yes and all locations of cancer reported are not within GI system)

Baseline risk factors of GI cancer include: history of cancer, history of individual GI conditions of special interest, history of adenomatous polyps of small intestine or colon prior to randomization, family history of intestinal cancer, and family history of adenomatous polyps.

12.7.5.3. GI procedures

The information on select GI procedures (which includes upper/capsule endoscopy, push enteroscopy, colonoscopy, sigmoidoscopy and other GI endoscopic procedures) from randomization to the end of study have been collected. Free text field in "Other" category will undergo clinical review before unblinding of database, and may be slotted into broad categories, such as Other – GI endoscopic, Other GI – non-endoscopic, etc.; clinical decision on such categorization will be deemed final. Only GI endoscopic procedures (select GI procedures as well as the free text field so categorized) will be included in summaries; other procedures in free text categories will remain the database,

but will not be summarized. All records of GI procedures with procedure date equal to or later than the randomization date will be included in the summaries.

The number and percentage of subjects, overall and by treatment group, who had a GI procedure conducted post-randomization (overall and by procedure) will be provided. For subjects reporting at least one GI procedure post-randomization, the number and percentage of subjects, overall and by treatment group, by reason for the procedure (overall and by procedure) will also be provided. It is to be noted that a procedure could have multiple reasons and will be counted under each of these reasons when identified as such. The summary of cancer identification and polyp/neoplasm (either benign or of unknown pathology) identification will be provided. If a subject had more than one procedure and has a cancer detected in at least one of them, he will be counted in the ‘cancer identification Yes’ category. If the subject has more than one procedure and had no cancer detected in any of them, and no record with ‘cancer identification=Unknown’, he will be counted in ‘cancer identification=No’ category. If a subject had more than one procedure and has no cancer detected in any of them, and has at least one record with ‘cancer identification=Unknown’, he will be counted in ‘cancer identification=Unknown’ category. Similar algorithm will be followed for polyp/neoplasm identification.

Since darapladib may increase the risk of GI side effects, there exists the possibility that subjects randomized to darapladib will undergo more frequent GI endoscopic testing, as compared to subjects on placebo, during the trial. The above summaries will help assess the extent of ascertainment bias due to GI procedures being done more frequently in the darapladib group.

12.7.6. Anaphylaxis Diagnoses

The number and percentage of subjects with anaphylaxis while on study will be summarized by treatment group. A Kaplan-Meier plot will be provided as a visual display of the time to anaphylaxis by treatment group. Additional details regarding a subject’s medical conditions, allergies, and symptoms related to the hypersensitivity reaction will be provided in a listing.

12.7.7. Liver Events

Standard GSK liver event summaries will be provided for subjects who have liver events while on study as required by the GSK Hepatotoxicity Board. The displays will only be produced when a liver event has occurred as defined in the protocol and the Liver Event Assessment forms on the eCRF have been completed. If the occurrence of liver events is extremely rare, listings will be used instead of summaries for the liver events data.

12.7.8. New Onset Albuminuria

New onset albuminuria is defined as a urine ACR result that is $\geq 30\text{mg albumin/g creatinine}$, occurring post-baseline for subjects who did not have albuminuria at baseline.

The number and percentage of subjects with new onset albuminuria will be summarized by treatment group. Additionally, summaries of new onset albuminuria will be provided for the following mutually exclusive subsets of subjects: diabetics at baseline, new onset

diabetics, and subjects with no diabetes diagnosis during the study. A Kaplan-Meier plot will be provided as a visual display of the time to new onset albuminuria by treatment group and descriptive measures will be produced consisting of a hazard ratio, 95% confidence interval, and p-value for the comparison of treatment groups.

13. HEALTH OUTCOMES ANALYSES

This study will measure health economic outcomes including medical resource utilization. The following data will be collected as part of clinical data collection to facilitate economic evaluation:

- All revascularization procedures and all amputations
- All hospitalizations with discharge diagnosis and length of stay
- Pharmacotherapy
- Mortality (including CV death, CHD death and all-cause death)

The health economic endpoints include:

- Total treatment cost (excluding costs incurred specifically to perform the trial)
- Cost per vascular event avoided
- Cost per life-year saved (LYS)
- Cost per quality-adjusted life-year (QALY) gained

The health utility and cost for events of interest are required for a complete economic evaluation. This information will be gathered from other sources (e.g., literature, database, or country-specific studies). Economic analyses will be produced using healthcare resource use from the United States and other selected countries as the basis for evaluation.

Details of these analyses will be described in a separate document.

14. CLINICAL PHARMACOLOGY DATA ANALYSES

14.1. Pharmacokinetic Analyses

See Section 18.4 for further details related to pharmacokinetic analyses.

14.2. Pharmacodynamic Analyses for Lp-PLA₂ Activity

Blood samples to assess Lp-PLA₂ activity will be obtained from all subjects at Baseline, and at Months 1, 3, 6, and 18 and End-of-Treatment/Early Withdrawal (note that subjects are not dosed on the day of the End-of-Treatment/Early Withdrawal Visit). Whenever possible, on-therapy samples should preferably be obtained at trough (24 ± 2 hours after the previous dose and immediately prior to the current dose). Lp-PLA₂ activity will be assessed for all Baseline samples and for a subset of post-Baseline samples (from approximately 5000 subjects). Subjects who have Lp-PLA₂ samples drawn at Screening to verify exclusion criteria related to Lp-PLA₂ activity will not have this sample re-drawn

at Baseline. Therefore, for these subjects who are randomized into the study the Screening samples will be used as the Baseline samples for pharmacodynamic analysis. Because Lp-PLA₂ levels can unblind treatment, the values will not be provided to investigators or to other blinded members of the study team during the course of the study.

The subjects whose on-treatment Lp-PLA₂ values (i.e., up to and including the day after the last dose of IP) will be assessed using post-baseline samples will include all subjects participating in the serial and trough PK substudies (see Section 11.8 in the study protocol for more details). The remaining subjects included in this subset will be selected at random, stratified by country with the number of subjects selected within each country proportional to the number of subjects randomized within that country. In countries where the number of PK subjects is more than the country's proportional allocation based on the number of subjects randomized, adjustments will be made on a regional level such that the regional allocation remains proportional to the regional randomization. This subset will be selected on blinded data after most of the subjects have been randomized into the trial. At the time of this selection, any subjects who have died, permanently discontinued IP, or who have withdrawn from the study will not be selected and the probability of selection will be higher for subjects who have completed later visits in an attempt to maximize the amount of post-baseline Lp-PLA₂ samples that will be available for assay.

It is anticipated that the Lp-PLA₂ activity will have a skewed distribution. If the data has a skewed distribution, values will be log transformed before analysis. Summary statistics will be calculated on the log transformed data and back transformed for presentation in summary tables. Summary statistics for Lp-PLA₂ activity will include n, geometric mean, 95% CI for geometric mean, median, minimum, maximum, and other appropriate percentiles.

Summaries of screening and baseline data will be provided for all subjects on the raw data without use of any transformations.

In the subset of subjects who have samples taken while on-treatment, summaries of Lp-PLA₂ activity will be provided at each available visit for each treatment group. Additionally, summaries of the change from baseline in Lp-PLA₂ activity will be provided at each available visit. These summaries will also be provided by region and by country. Graphical summaries may also be provided.

The time course of plasma Lp-PLA₂ activity will be characterized using the generalized estimating equations model with subject fitted as a random effect and terms included for treatment, visit, baseline value, treatment by visit, and baseline by visit interactions. An appropriate variance-covariance matrix will be used to model the correlation among visits within individual subjects. A point estimate, 95% confidence interval, and p-value for the mean difference between darapladib and placebo subjects at Month 18 (primary) and other time points (secondary) will be produced using this generalized estimating equations model. Treatment differences will be transformed and expressed as a percentage differences. Graphical summaries may also be provided.

The percentage Lp-PLA₂ inhibition relative to baseline will be calculated at each available visit. Similar summaries as provided above for change from baseline will be provided for percentage Lp-PLA₂ inhibition.

The baseline Lp-PLA₂ activity levels for all subjects will be used to define subgroups using tertiles (see Section 8.2). A subgroup analysis will be performed for the primary endpoint major coronary events as well as for MACE using a Cox proportional hazards model adjusted for treatment, baseline Lp-PLA₂ activity tertiles, and the interaction between treatment and the tertiles. Hazard ratios and 95% confidence intervals for the treatment effect for MACE will be provided for each Lp-PLA₂ tertile level.

A complimentary model will be performed for primary endpoint major coronary events as well as MACE using a Cox proportional hazards model adjusted for treatment, baseline Lp-PLA₂ activity (as a continuous variable), and the interaction between treatment and baseline Lp-PLA₂ activity.

See Section 11.1.1 for more details related to subgroups and the analysis of the primary endpoint.

14.3. Pharmacokinetic/Pharmacodynamic Analyses

See Section 18.4 for further details related to pharmacokinetic/pharmacodynamic analyses.

15. BIOMARKER DATA ANALYSIS

Blood samples to assess biomarkers of CV risk (may include, but are not limited to high-sensitivity troponin levels, high sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], and brain natriuretic peptide [BNP]) and other circulating biomarkers associated with atherosclerosis, coagulation, or related disease progression will be obtained at Baseline, Month 1, Month 6, and End of Treatment/Early Withdrawal. Biomarker analyses are considered exploratory and may be conducted in all subjects or in a subset of subjects.

Biomarkers will be summarized by treatment group at each visit using mean, standard deviation, median, minimum, maximum, and other appropriate percentiles. The change from baseline values will also be summarized by treatment group at each visit. Graphical summaries may also be provided. Details regarding planned biomarker analyses will be detailed in a separate analysis plan.

16. GENETIC DATA ANALYSES

Details of the analysis of genetic data will be specified in a separate Genetic Analysis Plan prior to conducting any genetic analysis.

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18. APPENDICES

18.1. Appendix 1: Laboratory Abnormal Ranges and Clinical Concern Ranges for Laboratory Tests

Table 8 Laboratory Abnormal Ranges and Clinical Concern Ranges for Laboratory Tests

Lab Parameter (Dataset ID)	Units	Age Categories (years)	Laboratory Ranges		Clinical Concern Ranges	
			Low flag (<x)	High flag (>x)	Low flag ($\leq x$)	High flag ($\geq x$)
Clinical Chemistry:						
Blood urea nitrogen	mmol/L	≤ 64 65+	2.5 2.5	9.0 10.5	NA	NA
	mg/dL	≤ 64 65+	7 7	25 30		
Calcium	mmol/L		2.12	2.56	2.0	2.88
	mg/dL		8.5	10.3	8.0	11.5
Chloride	mmol/L		95	108	75	115
	mEq/L		95	108	75	115
Serum Creatinine	$\mu\text{mol}/\text{L}$		44	124	NA	>265 or doubling from baseline
	mg/dL		0.5	1.4		>3.0 or doubling from baseline
eGFR	$\text{mL/sec}/1.73\text{m}^2$		NA	NA	NA	NA
Potassium	mmol/L		3.5	5.3	3.0	5.5
	mEq/L		3.5	5.3	3.0	5.5
Sodium	mmol/L		135	146	130	150
	mEq/L		135	146	130	150
Bicarbonate (CO ₂ Content)	mmol/L		20	32	NA	NA
	mEq/L		20	32		
Hemoglobin A1c	% TL HB		NA	6.4	NA	>10%
Glucose (fasting)	mmol/L		3.9	5.5	NA	NA
	mg/dL		70	99		
Lipids:						
Total Cholesterol	mmol/L	≤ 19 20+	0.00 0.00	4.35 5.15	NA	NA
	mg/dL	≤ 19 20+	0 0	170 200		

Lab Parameter (Dataset ID)	Units	Age Categories (years)	Laboratory Ranges		Clinical Concern Ranges	
			Low flag (<x)	High flag (>x)	Low flag (≤x)	High flag (≥x)
LDL, Calculated	mmol/L	≤19	0.00	2.83	NA	NA
		20+	0.00	2.57		
LDL, Direct	mmol/L	≤19	0.00	2.83	NA	NA
		20+	0.00	2.57		
HDL, Direct	mmol/L	≤19	0.9	NA	NA	NA
		20+	35	NA		
Triglycerides	mmol/L	≤19	0.00	2.24	NA	NA
		20+	0	200		
Non-HDL Cholesterol	mmol/L	≤19	NA	NA	NA	NA
		20+				
Liver Chemistry:						
Alkaline phosphatase	U/L	M: ≤19	30	225	NA	2.5 x ULN
		F: ≤19	30	165		
		20+	20	125		
ALT	U/L		0	48	NA	3 x ULN
AST	U/L	≤64	0	42	NA	3 x ULN
		65+	0	55		
Total Bilirubin	μmol/L	≤64	0	22	NA	2 x ULN
		65+	0.0	1.3		
Total Protein	g/L	≤64	60	85	NA	NA
		65+	58	81		
Serum Albumin	g/L	≤64	6.0	8.5	NA	NA
		65+	5.8	8.1		
	g/dL	≤64	32	50	NA	NA
		65+	3.2	5.0		
Hematology:						
Hematocrit	1 %	M: ≤64	0.410	0.500	NA	NA
		M: 65+	0.360	0.490		
		F: ≤64	0.350	0.460		
		F: 65+	0.330	0.460		
		M: ≤64	41.0	50.0		
		M: 65+	36.0	49.0		
		F: ≤64	35.0	46.0		
		F: 65+	33.0	36.0		

Lab Parameter (Dataset ID)	Units	Age Categories (years)	Laboratory Ranges		Clinical Concern Ranges	
			Low flag (<x)	High flag (>x)	Low flag (≤x)	High flag (≥x)
Hemoglobin	g/L	M: ≤64	138	172	100	185
		M: 65+	118	168		
		F: ≤64	120	156		
		F: 65+	111	155		
	g/dL	M: ≤64	13.8	17.2	10.0	18.5
		M: 65+	11.8	16.8		
		F: ≤64	12.0	15.6		
		F: 65+	11.1	15.5		
Platelet count	GI/L		130	400	100	600
White blood cell count	GI/L		3.8	10.8	3.0	20.0
Neutrophil count	GI/L		1.80	8.00	1.5	NA
Other:						
Hepatitis B surface antigen			Reactive		NA	NA
Hepatitis C antibody			Reactive		NA	NA
Urinalysis:						
Albumin/Creatinine Ratio (ACR)	mg/mmol mg/g		0.0 0	3.3 28.9	NA	NA

NA: Not applicable

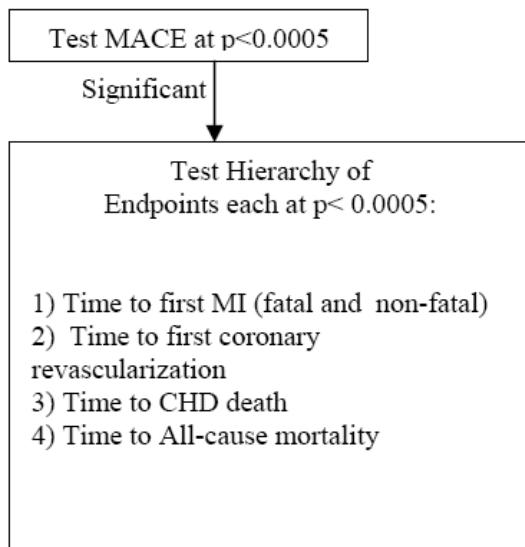
18.2. Appendix 2: Threshold Ranges for Vital Signs

Table 9 Threshold Ranges for Vital Signs

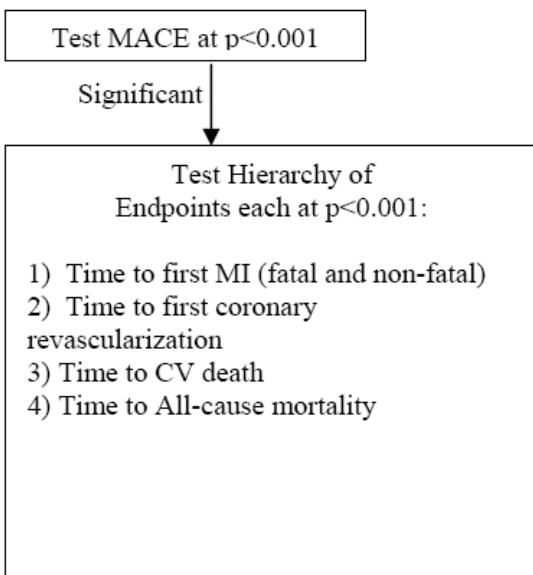
Vital Sign	Threshold Ranges Values of Clinical Concern		
	Units	Lower	Upper
Sitting Systolic blood pressure	mmHg	<90	>200
Sitting Diastolic blood pressure	mmHg	<40	>120
Sitting Heart rate	beats per minute	<50	>120

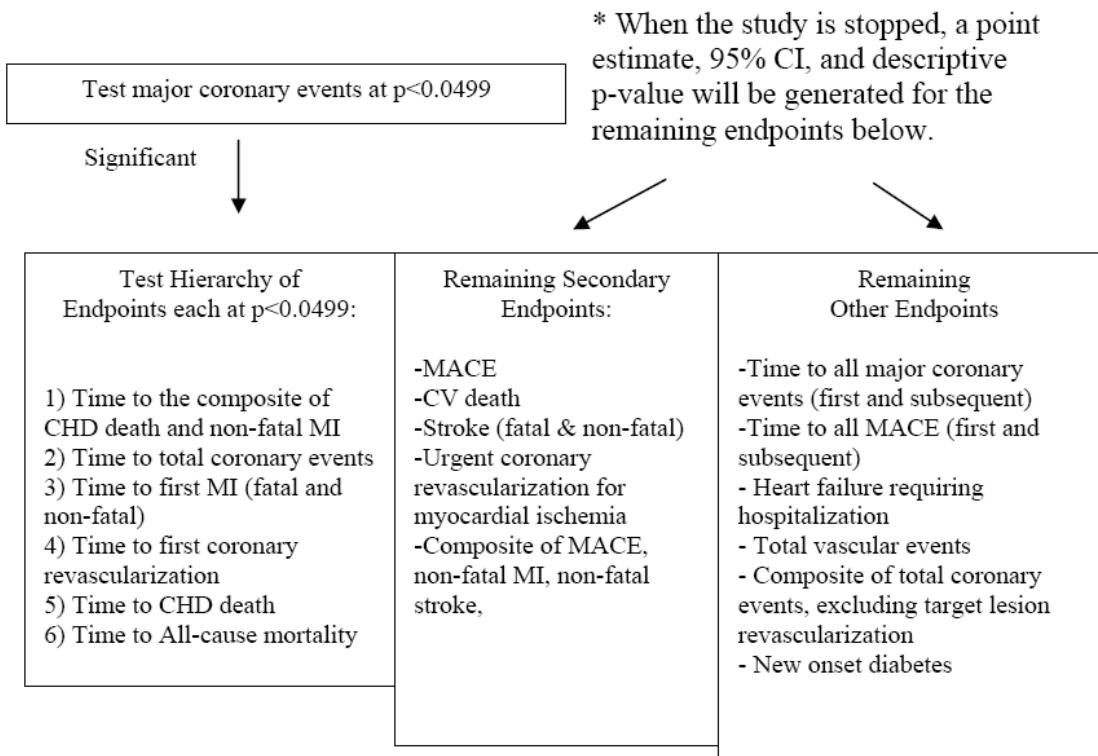
18.3. Appendix 3: Efficacy Endpoint Testing Strategy

Study Stopped* for Efficacy on MACE after Interim Analysis 1



Study Stopped* for Efficacy on MACE after Interim Analysis 2



Study Ends* at Planned Final Analysis

18.4. Appendix 4: Classification of Cancer Location

18.4.1. Specific Cancer Condition Noted in History of Cancer

Classification	Specific cancer condition
Gastrointestinal	Bile duct cancer
	Bowel cancer
	Esophageal cancer
	Gallbladder cancer
	Gastric cancer
	Liver cancer
Other	Pancreatic cancer
	Hodgkin's disease
	Leukemia
	Lymphoma
	Multiple myeloma
	Myelodysplastic syndrome
	Benign neoplasm
	Bladder cancer
	Breast cancer
	Cervical cancer
	Endometrial cancer
	Fallopian tube cancer
	Lip cancer
	Lung cancer
	Non-melanoma skin cancer
	Oral cancer
	Ovarian cancer
	Penile cancer
	Pharyngeal cancer
	Prostate cancer
	Renal cancer
	Scrotum cancer
	Skin melanoma
	Testicular cancer
	Vaginal cancer
	Vulval cancer

18.4.2. Primary Location of Cancer Reported by Investigator

Classification	Location of primary cancer
Small Intestine	Lymphoma small intestinal origin
	Small intestinal adenocarcinoma
	Small intestinal carcinoid tumors
	Small intestinal sarcoma
	Small intestine cancer other, specify
Large Intestine	Colon cancer
	Colorectal cancer
	Rectal cancer
Small/Large Intestine – Region Unknown	Bowel cancer - region unknown
GI excluding small/large intestine	Bile duct cancer
	Bowel cancer - region unknown
	Esophageal cancer
	Gastric cancer
	Gallbladder cancer
	Liver cancer
	Lymphoma gastric origin
	Lymphoma other gastrointestinal
	Pancreatic cancer
	Gastrointestinal carcinoid tumor
	Gastrointestinal stromal tumor (GIST)
	Hodgkin's disease gastrointestinal involvement
	Other gastrointestinal cancer, specify
Other	Anal Cancer
	Hodgkin's disease, no gastrointestinal involvement
	Myelodysplastic syndrome
	Leukemia
	Multiple myeloma
	Benign non-gastrointestinal neoplasm
	Bladder cancer
	Bone cancer
	Brain cancer
	Breast cancer
	Cervical cancer
	Endometrial cancer
	Fallopian tube cancer
	Larynx cancer
	Lip cancer
	Lung cancer
	Lymphoma non-gastrointestinal

Classification	Location of primary cancer
	Mesothelioma
	Oral cancer
	Ovarian cancer
	Penile cancer
	Pharyngeal cancer
	Prostate cancer
	Renal cancer
	Scrotum cancer
	Skin cancer, melanoma
	Skin cancer non-melanoma
	Spinal cord
	Testicular cancer
	Thyroid cancer
	Uterine, other site
	Vaginal cancer
	Vulval cancer
	Other cancer site, specify
Unknown	Unknown primary cancer

18.4.3. Location of Primary GI Cancer Reported in Adjudication

Classification	Primary GI Cancer Location (adjudicated)
Small Intestine	Adenocarcinoma - Small Intestine
	Signet ring cell carcinoma - Small Intestine
	Squamous cell carcinoma - Small Intestine
	Undifferentiated carcinoma - Small Intestine
	Neuroendocrine tumor (NET) - NET G1 (carcinoid) - Small Intestine
	Neuroendocrine carcinoma (NEC) - Small Intestine
	EC cell, serotonin-producing NET - Small Intestine
	Gastrinoma - Small Intestine
	L-cell, Glucagon-like peptide-producing and PP/PYY-producing NETs - Small Intestine
	Gastrointestinal stromal tumor - Small Intestine
	Gastrointestinal stromal tumor - Small Intestine
	Leiomyosarcoma - Small Intestine
	Leiomyoma - Small Intestine
	Lipoma - Small Intestine
	Other - Small Intestine
Large Intestine	Adenocarcinoma - Appendix
	mucinous adenocarcinoma, Low-grade appendix
	Signet ring cell carcinoma - Appendix
	Undifferentiated carcinoma - Appendix
	Neuroendocrine tumor (NET) - NET G1 (carcinoid) - Appendix
	Neuroendocrine carcinoma (NEC) - Appendix
	Other - Appendix
	Adenocarcinoma - Colon and rectum
	Adenocarcinoma - Signet ring cell carcinoma - Colon and rectum
	Adenocarcinoma - Undifferentiated carcinoma - Colon and rectum
	Neuroendocrine tumor (NET) - NET G1 (carcinoid) - Colon and rectum
	Neuroendocrine carcinoma - Colon and rectum
	EC cell, serotonin-producing NET - Colon and rectum
	L-cell, Glucagon-like peptide-producing and PP/PYY-producing NETs Colon & rectum
	Gastrointestinal stromal tumor - Colon and rectum
	Leiomyosarcoma - Colon and rectum
	Leiomyoma - Colon and rectum
	Lipoma - Colon and rectum
	Other - Colon and rectum

Classification	Primary GI Cancer Location (adjudicated)
GI excluding small/large intestine	Glucagonoma
	Hepatocellular carcinoma
	Hepatocellular carcinoma, fibrolamellar variant
	Insulinoma
	Intrahepatic cholangiocarcinoma
	Pancreatic intraepithelial neoplasia, grade 3 (PanIN-3)
	Adenocarcinoma - Esophagus
	Squamous cell carcinoma - Esophagus
	Undifferentiated carcinoma - Esophagus
	Neuroendocrine tumor (NET) - Esophagus
	Neuroendocrine carcinoma (NEC) - Esophagus
	Gastrointestinal stromal tumor - Esophagus
	Leiomyosarcoma - Esophagus
	Leiomyoma - Esophagus
	Lipoma - Esophagus
	Other - Esophagus
	Adenocarcinoma - Stomach
	Squamous cell carcinoma - Stomach
	Undifferentiated carcinoma - Stomach
	Neuroendocrine tumor (NET) – NET G1 (carcinoid) - Stomach
	Neuroendocrine carcinoma (NEC) - Stomach
	Gastrointestinal stromal tumor - Stomach
	Leiomyosarcoma - Stomach
	Leiomyoma - Stomach
	Lipoma - Stomach
	Other - Stomach
	Adenocarcinoma - Ampullary region
	Signet ring cell carcinoma - Ampullary region
	Undifferentiated carcinoma - Ampullary region
	Neuroendocrine tumor (NET) - NET G1 (carcinoid) - Ampullary region
	Neuroendocrine carcinoma (NEC) - Ampullary region
	Somatostatin-producing NET - Ampullary region
	Other - Ampullary region
	Neuroendocrine carcinoma (NEC) - Appendix
	Adenocarcinoma - Anal canal
	Squamous cell carcinoma - Anal canal
	Undifferentiated carcinoma - Anal canal
	Other - Anal canal
	Undifferentiated carcinoma - Liver & Intrahepatic bile ducts

Classification	Primary GI Cancer Location (adjudicated)
	Other - Liver & Intrahepatic bile ducts
	Adenocarcinoma - Gallbladder & extrahepatic bile ducts
	Neuroendocrine tumor (NET) - NET G1 (carcinoid) - Gallbladder & extrahepatic bile ducts
	Neuroendocrine carcinoma (NEC) - Gallbladder & extrahepatic bile ducts
	Other - Gallbladder & extrahepatic bile ducts
	Signet ring cell carcinoma - Pancreas
	Undifferentiated carcinoma - Pancreas
	EC cell, serotonin-producing NET (carcinoid) - Pancreas
	Gastrinoma - Pancreas
	Other - Pancreas
	Acinar cell cystadenocarcinoma
	Adenoid cystic carcinoma
	Adenosquamous carcinoma
	Angiosarcoma
	Ductal adenocarcinoma
	Epithelioid haemangioendothelioma
	Gastrin-producing NET (gastrinoma)
	Intraductal papillary mucinous neoplasm with an associated invasive carcinoma
	Intraductal papillary mucinous neoplasm with high-grade dysplasia
	Neuroendocrine carcinoma (NEC) Large cell
	Poorly cohesive carcinoma (including signet ring cell carcinoma and other varian
	Serous cystadenocarcinoma
	Somatostatinoma
	Teratoma
	Verrucous carcinoma
	VIPoma
	Yolk sac tumor (endodermal sinus tumor)
<u>Unknown</u>	<u>Unknown</u>

18.5. Appendix 5: Analysis Plan for the Population PK Substudies

The following is a brief summary of the goals of the population PK substudies and the PK/PD analyses with data specifications necessary for the analysis of the population PK substudy data. Full analyses specific to the population PK substudies are provided in the Data Analysis Plan (DAP) as a separate document.

Population PK and PK/PD analyses will be the responsibility of the Department of Clinical Pharmacology Modeling & Simulation (CPMS), Quantitative Sciences, GlaxoSmithKline.

18.5.1. Population PK Substudy Objectives

Primary

Establish a population PK model adequate to describe the time-course and variability of plasma darapladib concentrations following repeat dose administration of EC tablets, 160 mg in patients with ACS.

Secondary

Establish a population PK/PD model adequate to describe the relationship between plasma darapladib concentration and plasma Lp-PLA₂ activity following repeat dosing of EC tablets, 160 mg in patients with ACS.

18.5.2. Population PK Substudy Design

These PK/PD substudies are multicenter substudies of the SOLID-TIMI 52 study (the parent study). Centers participating in the parent study will be invited to participate in the PK/PD substudies. Subjects who qualify for the parent study and provide signed written informed consent to participate in a PK/PD substudy are eligible.

Blood samples for darapladib PK analysis and blood samples for Lp-PLA₂ activity analysis will be collected into purple-top tubes and immediately chilled on crushed ice at the following time points, relative to dosing:

1. Serial Samples PK Substudy collected at Month 3 and Month 18 at trough (24 ± 2 hours after the previous dose and immediately prior to the current dose); 1, 2, 3, and 4 hours ± 15 minutes after the current dose; and 6, 8, and 24 hours ± 30 minutes after the current dose.
2. Trough Sample PK Substudy collected at Months 1, 3, 6, and 18 at trough (24 ± 2 hours after the previous dose and immediately prior to the current dose).

For both sampling schemes, the exact time of sample collection will be recorded in the GSK-defined eCRF. The exact time of dosing on the day of the visit, 1 day prior to the visit and 2 days prior to the visit will be recorded in the eCRF by having the subject return a medication card on which the subject records this information.

18.5.3. Pharmacokinetic Analysis

Initially, a base population PK model (i.e., without inclusion of covariates) will be developed using data from the Phase III patients who contributed serial PK samples over a 24-hour period. The Phase III data may be combined with selected healthy volunteer data (e.g., studies using the same dose and administering the EC, micronized free base tablet with food). Next, an exploratory analysis will be conducted on the relationship between PK parameters from the base population PK model and various covariates.

Significant covariate-parameter relationships will then be incorporated into the population PK model. An evaluation of the final population PK model will be performed. It is also planned to perform a non-compartmental analysis using the full concentration-time profiles collected from the Phase III patients. These results could be used to perform a posterior predictive check of the final population PK model.

Alternatively, in case a robust population PK model cannot be developed, the non-compartmental analysis will provide AUC and Cmax data for darapladib in the target patient population which can be further explored for the influence of potential covariates. Data from the multiple-trough sampling design will be analyzed by mixed effects modeling.

PK data will be analyzed using the nonlinear mixed effects modeling program (NONMEM). 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 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 intra-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.

Further details of the analysis of pharmacokinetic data will be provided in a separate analysis plan.

18.5.4. Pharmacokinetic/Pharmacodynamic Analysis

The relationship between plasma concentrations of darapladib and plasma Lp-PLA₂ activity in humans has been explored using data obtained from previous studies. This concentration-effect relationship was best characterized by a sigmoidal inhibitory Emax model. This structural model was parameterized for IC50, the darapladib plasma concentration causing 50% inhibition of plasma Lp-PLA₂ activity (ng/mL), E0, the baseline plasma Lp-PLA₂ activity (nM/min/mL) and γ , the Hill coefficient which describes the steepness of concentration-effect relationship. In the current study, a similar structural PK/PD model will be utilized to estimate parameters specific to the patient population of this study. Various statistical models will be examined to describe the variability of the data and parameterized as appropriate.

PK/PD data will be analyzed with the use of the nonlinear mixed effects modeling program (NONMEM). Model selection will be conducted using the same criteria as described above for the PK analyses. Covariates examined during the development of the population PK model will also be evaluated to assess their effects on darapladib PK/PD.

Further details of the analysis of pharmacokinetic/pharmacodynamic data are provided in the Data Analysis Plan as a separate document.

18.5.5. Population PK and PK/PD Reporting Strategy

The population PK and PK/PD analyses will be reported as a stand-alone report.

18.6. Appendix 6: Summary of Country-specific Analysis Requirements

Additional summaries will be generated for certain subgroups in order to provide more detailed information on subjects related to regulatory requirements in various countries. These summaries will be similar to those already described in the main body of this document, but will simply include the specified subsets of subjects. Since the number of subjects available for country-specific analyses is small relative to the full complement of subjects, it is recognized that hypothesis testing may be drastically underpowered. Details of these additional summaries will be described in a separate document.

18.7. Appendix 7: Analysis Plan for the Obstructive Sleep Apnea Substudy

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive pharyngeal collapse during sleep [Malhotra, 2002]. Although publications suggest that approximately 4% of men and 2% of women in the United States have symptomatic sleep apnea (19), these figures are likely underestimates. Based on the aging of the population and the obesity pandemic, the prevalence of OSA has likely increased since these data were published. In addition, recent improvements in diagnostic technology imply that apnea prevalence may be considerably higher than the original estimates. Additionally, the recognition that even asymptomatic apnea can have negative health consequences is prompting earlier diagnosis. Notwithstanding the exact prevalence of the disease, sleep apnea represents a major public health problem based on its rising prevalence and its well established neurocognitive and cardiovascular sequelae [Malhotra, 2009, Teran-Santos, 1999].

Prior literature questioned the importance of OSA due to the considerable comorbidities associated with disease [Wright, 1997]. Since cardiovascular disease and OSA share common risk factors such as obesity, diabetes mellitus, hypertension, some authors concluded that OSA was simply a marker of an unhealthy individual (epiphenomenon) rather than a causative risk factor [Wright, 1997]. Consequently, many studies were undertaken in the past decade and considerable data has emerged that confirm that OSA has a causal role in the development of cardiovascular disease [Becker, 2003; Brooks, 1997; Lavie, 2000; Peppard, 2000; Pepperell, 2002]. For example, several lines of evidence indicate that OSA causes systemic elevations in blood pressure. First, elegant animal models have shown that induction of apnea can yield systemic elevations in blood pressure [Brooks, 1997]. Elimination of apnea leads to normalization of blood pressure, strongly suggesting that apnea per se can lead to daytime elevation of blood pressure in animal models [Pepperell, 2002]. Second, large epidemiological human studies have shown a robust association between sleep apnea and hypertension, independent of known confounding variables [Hayashi, 2000; Lavie, 2000; Peppard, 2000]. Longitudinal studies have shown a tripling of incidence of hypertension in patients with even moderate sleep apnea, again independent of any known covariates [Peppard, 2000]. Third, a variety of therapeutic studies have shown that nasal continuous positive airway pressure (CPAP) treatment of OSA can lead to major improvements in daytime blood pressure, particularly among adherent patients with baseline hypertension [Becker, 2003; Faccenda, 2001]. Thus, OSA is now considered a risk factor for hypertension.

Associations between sleep apnea and other cardiovascular outcomes such as MI, stroke and congestive heart failure remain more speculative [Shahar, 2001]. The Sleep Heart Health Study (SHHS) examined the hypothesis that sleep apnea would lead to important elevations of risk of major cardiovascular outcomes. Although cross-sectional data showed some association between OSA and cardiovascular outcomes, the longitudinal outcome data are less compelling [Punjabi, 2009]. The reason for this SHHS finding is somewhat unclear, but may reflect a relatively mild severity of illness, a high age of participants, and largely asymptomatic nature of the cohort. Several other studies have shown that OSA increases the incidence of stroke and other cardiovascular abnormalities, independent of known covariates [Arzt, 2005; Yaggi, 2005]. However, randomized

controlled trials demonstrating that treatment of OSA can prevent major cardiovascular endpoints such as MI, congestive heart failure and cerebrovascular accident (stroke) do not exist but are ongoing. Association studies have shown that CPAP adherent patients have an improved outcome over those who are non-adherent [Marin, 2005]. Two different interpretations emerge from this finding. Some argue that these data show that CPAP improves cardiovascular outcomes, which is biologically possible although as yet unproven. On the other hand, CPAP adherent patients may be different from non-adherent patients for reasons apart from CPAP [Platt, 2010]. For example, adherent patients may be more motivated and better educated individuals and thus may be more compliant with medications, diet and exercise as compared with non-adherent individuals. Therefore, randomized clinical trials will be required to draw definitive conclusions, although such studies are logically and ethically challenging [Malhotra, 2009].

18.7.1. Obstructive Sleep Apnea Substudy Objectives

The Obstructive Sleep Apnea substudy is designed to test the association between risk of obstructive sleep apnea and incidence of major adverse cardiovascular events (MACE) in subjects following acute coronary syndrome.

18.7.2. Obstructive Sleep Apnea Substudy Endpoints

The primary endpoint to be analyzed in the sleep study is the time to the first occurrence of any component of the composite of **MACE**, which consists of the following:

- CV death
- Non-fatal MI
- Non-fatal stroke

The secondary endpoints are:

- First occurrence of composite of MACE and All-cause Mortality
- First occurrence of Myocardial Infarction (MI) – fatal and non-fatal
- First occurrence of Stroke – fatal and non-fatal
- First occurrence of urgent coronary revascularization

18.7.3. Obstructive Sleep Apnea Substudy Design

All subjects who qualify for the SOLID-TIMI-52 study will be asked to participate in the obstructive sleep apnea substudy at the baseline visit by completing the Berlin Questionnaire [Netzer, 1999].

18.7.3.1. Obstructive Sleep Apnea Substudy Assessments

Efficacy data for MACE will be assessed per the study protocol, and is described in detail in the main study RAP.

Other covariates to be used for sleep study are as follows:

- Obstructive Sleep Apnea (OSA) Risk Status
- Overnight Work Shift History (OWSH)
- Average hours of sleep per day
- Neck circumference
- History of Sleep Apnea

The Berlin Questionnaire [Netzer, 1999] will be used to assess the risk of obstructive sleep apnea; a copy of this questionnaire is enclosed with this analysis plan. The Berlin Questionnaire assesses known risk factors and symptoms of OSA: snoring and pauses in breathing (Category 1), daytime sleepiness/fatigue (Category 2), and history of high blood pressure and/or body mass index (BMI) greater than 30 (Category 3). Category 1 and Category 2 questions were included in the eCRF as a separate assessment for sleep study; blood pressure and BMI are taken from the baseline assessment for the overall study.

Each question is scored as 1 or 0 as follows (0 is designated for non-missing response not scored as 1 or a missing response):

Category 1 (Snoring/pauses in breathing):

Q2. Snore? ‘Yes’ is scored as 1.

Q3. Snore loudness: ‘Louder than talking’ or ‘Very loud’ is scored as 1 when Q2=’Yes’.

Q4. Snore frequency: ‘Nearly every day’ or ‘3-4 times a week’ is scored as 1 when Q2=’Yes’.

Q5: Snore bother: ‘Yes’ is scored as 1 when Q2=’Yes’.

Q6: Quit breathing in sleep: ‘Nearly every day’ or ‘3-4 times a week’ is scored as 1 when Q2=’Yes’.

Category 2 (Daytime sleepiness/fatigue):

Q7. Fatigue after sleep: ‘Nearly every day’ or ‘3-4 times a week’ is scored as 1.

Q8. Fatigue during wake hours: ‘Nearly every day’ or ‘3-4 times a week’ is scored as 1.

Q9. Sleepy during driving: ‘Nearly every day’ or ‘3-4 times a week’ is scored as 1.

Category 3 is evaluated as follows:

Baseline vital sign value is the last available values of the vital sign on or before randomization date. If the baseline diastolic blood pressure is >120mmHg or baseline systolic blood pressure is >200mmHg then Q10 in Berlin questionnaire is considered Yes, and is scored as 1; otherwise the score on blood pressure is 0. If the baseline BMI >30 then BMI score is 1; otherwise BMI score is 0.

Total score on each category is the sum of scores on questions in that category. If the score in Category 1 and Category 2 is ≥ 2 , or the score in Category 3 is ≥ 1 (either high blood pressure or high BMI) then the subject is defined to be positive for the specific

category. OSA risk status for a subject is defined as High if the subject has two or more positive categories (called high likelihood of sleep disordered breathing in Berlin Questionnaire); otherwise the subject is defined as having OSA risk status as Low.

In addition to Berlin questionnaire, data have been collected on:

1. How many years one has worked on at least a) 3 overnight shifts per week, b) at least one overnight shift per week, where overnight shift is defined as at least 6 hours of work between 10 pm and 8 am. Subjects responding as 0 year (indicating either no such year of work or less than 1 year) or ‘Not applicable’ are categorized as No; subjects with response of ≥ 1 year is marked as Yes.
2. Hours of sleep, on average, within a 24 hour period. A subject will be categorized as <6 hours and ≥ 6 hours of sleep.

Two covariates that may affect efficacy will also be considered:

- 1) Sleep apnea reported at baseline – yes/No. This data has been collected as part of medical history.
- 2) Neck circumference at baseline, categorized as high/low: neck circumference (in cm) has been collected at baseline; high neck circumference is defined as ≥ 16 inches (i.e. >40.64 cm) for women and ≥ 17 inches (i.e. 43.18cm) for men.

18.7.4. Obstructive Sleep Apnea Substudy Population

All randomized subjects constitute the ITT population for the main study; this is the population that will be used for OSA substudy.

18.7.5. Obstructive Sleep Apnea Substudy Analyses

Refer to main study RAP regarding event inclusion, censoring, etc. of CV endpoints.

All time-to-event analyses will follow the analysis strategy described for MACE in Section 11.2. All analyses will be performed using the All Randomized (ITT) population with adjudicated events reported within the follow-up period for CV events. The risk will be estimated using the hazard ratio, the corresponding 95% confidence interval. P-value will be evaluated at a nominal 5% significance level, when provided. Kaplan-Meier survival curves will display the time to first MACE.

OSA risk question responses, OSA risk status and neck circumference at baseline will be summarized by treatment group and overall. In addition, neck circumference will be summarized by risk status.

18.7.5.1. Primary Analyses

The primary analysis will be restricted to the ITT subjects who were randomized to placebo. Time-to-event analysis will be performed on the time to first occurrence of MACE using a Cox proportional hazards regression model with OSA Risk Status as the only covariate in the model. The number and percentage of subjects with a MACE and

the number censored at the end of the study will be displayed along with the results of the Cox proportional hazards model. A Kaplan-Meier survival curve will be created to provide a graphical display of time to MACE by the OSA Risk Status.

18.7.5.2. Other Endpoints Analyses

Time-to-event analysis will be performed on the time to first occurrence of MACE using a Cox proportional hazards regression model with treatment, OSA Risk Status, and treatment by OSA Risk Status interaction included in the model. Hazard ratio and 95% confidence interval will be provided for treatment comparison within each OSA risk status; interaction p-value will be provided.

Time-to-event analysis will also be performed on the time to first occurrence of MACE using a Cox proportional hazards regression model with treatment and OSA Risk Status as covariates. Hazard ratio with 95% confidence interval for main effect of treatment as well as OSA risk status will be provided, along with chi-square p-value for significance of the hazard ratio. It is important to note that this summary will be interpreted only if the interaction term in the above model is less than 0.05; otherwise, this model will not be used for interpretation.

The same analyses will be conducted swapping OSA Risk Status with

- 1) Overnight Work Shift History – at least 3 shifts per week.
- 2) Overnight Work Shift History – at least 1 shift per week.
- 3) Average sleep: <6 hours, >=6 hours
- 4) Neck circumference: High, Low

The relationship between OSA risk status and neck circumference categories will be assessed by Chi-square test for association.

Time-to-event analysis will be performed on the time to first occurrence of MACE using a Cox proportional hazards regression model with OSA Risk Status and neck circumference as covariates, using the placebo treatment group only.

Time-to-event analysis will be performed on the time to first occurrence of MACE using a Cox proportional hazards regression model with treatment as the only covariate, separately within the subjects who reported a medical history of sleep apnea and who denied having a history of sleep apnea.

For primary endpoint as well as secondary endpoints, the number and percentage of subjects with each endpoint will be provided by treatment group and by:

- 1) OSA risk status – High / Low
- 2) Neck circumference – High / Low

18.7.6. Berlin Questionnaire

Berlin questionnaire**SLEEP EVALUATION**

1 Complete the following:

height _____ age _____
 weight _____ male/female _____

CATEGORY 1 2 Do you snore?

- yes
 no
 don't know

If you snore:

3 Your snoring is?

- slightly louder than breathing
 as loud as talking
 louder than talking
 very loud. Can be heard in adjacent rooms.

4 How often do you snore?

- nearly every day
 3-4 times a week
 1-2 times a week
 1-2 times a month
 never or nearly never

5 Has your snoring ever bothered other people?

- yes
 no

6 Has anyone noticed that you quit breathing during your sleep?

- nearly every day
 3-4 times a week
 1-2 times a week
 1-2 times a month
 never or nearly never

Scoring Questions: Any answer within box outline is a positive response.

Scoring Categories: Category 1 is positive with 2 or more positive responses to questions 2-6 Category 2 is positive with 2 or more positive responses to questions 7-9 Category 3 is positive with 1 or more positive responses and/or a BMI>30

Final Results: 2 or more positive categories indicates a high likelihood of sleep disordered breathing.

Name _____
Address _____

CATEGORY 2

7 How often do you feel tired or fatigued after your sleep?

- nearly every day
 3-4 times a week
 1-2 times a week
 1-2 times a month
 never or nearly never

8 During your wake time, do you feel tired, fatigued or not wake up to par?

- nearly every day
 3-4 times a week
 1-2 times a week
 1-2 times a month
 never or nearly never

9 Have you ever nodded off or fallen asleep while driving a vehicle?

- yes
 no

If yes, how often does it occur?

- nearly every day
 3-4 times a week
 1-2 times a week
 1-2 times a month
 never or nearly never

CATEGORY 3

10 Do you have high blood pressure?

- yes
 no
 don't know

BMI =

EDWARD

18.7.7. Obstructive Sleep Apnea Substudy References

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